A Model Structure for Advancing Rare Diseases Research

April 16, 2013
Jeffrey Krischer, PhD
RDCRN Overview

- Established by the Office of Rare Diseases Research
- 2003--10 Consortia supported by ORDR, NCRR, NINDS, NIAMS, NICHD, NHLBI, NIDDK
- 2009--17 Consortia supported by ORDR, NINDS, NIAMS, NICHD, NHLBI, NIDDK, NIAID, NIDCR, NCI
- 192 institutions around the world
- 2,290 consortium members
- 90+ patient advocacy groups
- 174 trainees
- 87 accruing studies
Goals of the RDCRN

• Facilitate clinical research by:
  – Creation of Consortia focused on related diseases
  – Cost-sharing research infrastructures
  – Establishing uniform protocols for data collection
  – Making meaningful large-scale studies possible
    • Longitudinal cohorts, pilot projects, and randomized trials

• Directly engage patients and their advocates

• Train new investigators in rare diseases research
- Collaborative Clinical Research
- Public Resources and Education
- Centralized Data Coordination and Technology Development
- Training

ORDR, NINDS, NIAMS, NICHD, NHLBI, NIDDK, NIDCR, NIAID, NCI

Coalition of Patient Advocacy Groups (CPAG)

Primary Immune Deficiency Treatment Consortium

Angelman, Rett & Prader-Willi Syndromes Consortium

Lysosomal Disease Network

NAMDC (North American Mitochondrial Disease Consortium)

The Data Management and Coordinating Center

Genetic Diseases of Mucociliary Clearance Consortium

Autonomic Disorders Consortium

Salivary Gland Carcinoma Consortium

Chronic Graft Versus Host Disease Consortium

The Porphyrias Consortium

Rare Kidney Stone Consortium

RARE CLINICAL DISEASES RESEARCH NETWORK

NATIONAL INSTITUTES OF HEALTH

Urea Cycle Disorders Consortium

Inherited Neuropathies Consortium
• Collaborative Clinical Research
• Centralized Data Coordination and Technology Development
• Public Resources and Education
• Training

Collaborative Clinical Research
Centralized Data Coordination and Technology Development
Public Resources and Education
Training

Collaborative Clinical Research
Centralized Data Coordination and Technology Development
Public Resources and Education
Training

Dystonia Coalition

Coalition of Patient Advocacy Groups (CPAG)

Chronic Graft Versus Host Disease Consortium

North America Mitochondrial Diseases Consortium

Primary Immune Deficiency Treatment Consortium

The Data Management and Coordinating Center

Rare Kidney Stone Consortium

Nephrotic Syndrome Rare Disease Clinical Research Network

Angelman, Rett and Prader-Willi Syndromes Consortium

Brain Vascular Malformation Consortium

ORDR, NINDS, NIAMS, NICHD, NHLBI, NIDDK, NIDCR, NIAID, NCI

Dysautonomia Coalition

Genetic Disorders of Mucociliary Clearance Consortium

Porphyria Rare Disease Clinical Research Consortium

Vasculitis Clinical Research Consortium

Lysosomal Disease Network

Inherited Neuropathies Consortium

Urea Cycle Disorders Consortium

Molecular and Epidemiologic Characterization of Salivary Gland Carcinomas Consortium

Sterol and Isoprenoid Diseases Consortium

Autonomic Rare Diseases Clinical Research Consortium
Basic Units of the RDCRN: DMCC & Rare Disease Consortia
(Only 2 of 17 Consortia shown for clarity)
RDCRN U.S. Sites
RDCRN International Sites

- Australia (INC)
- Belgium (DC)
- Canada (BVMC, DC, LDN, MCC, NAMDC, NEPTUNE, PIDTC, RKSC, STAIR, UCDC, VCRC)
- England (DC, INC)
- France (DC, RKSC)
- Germany (DC, INC, RKSC, UCDC)
- Iceland (RKSC)
- India (DC)
- Italy (DC, INC, RKSC)
- Netherlands (DC, RKSC)
- Scotland (DC)
- Spain (RKSC)
- Switzerland (UCDC)
Basic Units of the RDCRN: DMCC & Rare Disease Consortia

(Only 2 of 17 Consortia shown for clarity)
Data Management and Coordinating Center (DMCC)

- Supports RDCRN by providing technologies, tools, and support of study design and data analysis
- On-line protocol management system
  - Patient enrollment/randomization
  - Data entry and collection with data standards
  - Adverse event reporting
- Protocol training for research staff
- Members’ website: documentation, databases
- Hosts RDCRN public website (>3 million hits/year)
- Oversees the RDCRN Patient Contact Registry
RDCRN Website
http://rarediseasesnetwork.org

- Portal to websites for each Consortium
- Portal to members’ website
- Portal for patient advocacy groups
- RDCRN Contact Registry
- 3+ million hits/yr
DMCC Technologies/Tools

• Web-based data management system
  – Public Website
  – Consortium Portal
  – Full Study Support
• Adverse event reporting and review
• Specimen Tracking
  – Collection, Shipment, Receipt
• Pharmacy System
  – Treatment assignment, inventory, dose management
• Patient Contact Registry
Study Design and implementation

• Identifying population to draw from.
• Estimating event rates.
• Genotype-phenotype correlations.
• Hypothesis testing.
Members’ Website Resources

• Automated Slide Sets
• RDCRN Power Point Template Slides
• RDCRN, NIH and Consortium Logos
• Reports (Network, Consortium, Protocol level)
• Visiting Professorship Application Form
• Lecture Log
• Training (ClinicalTrials.gov, Audit, GCP, Ethics, etc.)
• Regulatory Templates (protocol, ICF, MOO, eCRFs)
RDCRN Contact Registry
Data as of April 3, 2013

- Over 120 diseases*
- 95 countries
- 11,279 total registrations*
- 42% from PAGs
- 40% from internet
- 7% from medical profess.

Goals:
To inform registrants about RDCRN studies available;
To disseminate information about RDCRN activities

*Excluding former consortia diseases/registrations (BMF, CINCH, CLiC, CRC-SCA, GSD, RLD, RTD)
Charcot Marie Tooth International Database (CMT-ID) Overview

- International registry database for patients with inherited neuropathies
- Will allow investigators to acquire standardized clinical data on patients throughout the world
- Will greatly facilitate the ability to develop common approaches and definitions to characterize CMT genotypes and phenotypes
- Will facilitate development of new clinical trials and, eventually, treatments

Sites that have been activated for CMT-ID:
- South Korea
- Brazil
- Australia
- Lebanon

Sites that are pursuing activation:
- Italy
- Germany
- United Kingdom
- Hungary
- Morocco
- New Zealand
- Canada
12 consortia are participating in the CR data sharing feature (ARD, BVMC, cGVHD, INC, LDN, NAMDC, NEPTUNE, PC, PIDTC, RKSC, STAIR, UCDC)

2,744 registrants have opted to share their information (168 with Consortia and others)

Share with consortia and others went live 06/27/12
Guidance

Steering Committee

RDC Center

Data Management and Coordinating Center

U.S. DHHS, NIH
NCATS, ORDR, NCI, NIAMS, NIDCR
NICHD, NHLBI, NIDDK, NINDS, NIAID

DSMB

Site

Site

Site

Site

Site

Site
Patient Interactions

- Patients
- Registries
- Support Groups
- CPAG
- Site
- RDC Center
- Contact Registry
- Public Website
Development of Clinical Study Protocols

Patients

Support Groups

RDC Centers

Site

Data Management and Coordinating Center

Clinical Data Standardization Groups

DSMB

U.S. DHHS, NIH
NCATS, ORDR, NCI, NIAMS, NIDCR
NICHD, NHLBI, NIDDK, NINDS, NIAID

Site
Standardization of Clinical Research Data

U.S. DHHS, NIH
NCATS, ORDR, NCI, NIAMS, NIDCR
NICHD, NHLBI, NIDDK, NINDS, NIAID

Data Management and Coordinating Center

RDCRN Committees

Clinical Data Standardization Groups

DSMB

Clinical Research Data Bank
Public Access to Rare Disease Information

Data Management and Coordinating Center

RDC Center

Site
Site
Site

Public Website

Media Library

Clinical Research Data Bank

Patient Community

Pharmaceutical Companies

Doctors
Researchers
Educators
How well does it work?
RDCRN2 Accomplishments
2nd grant cycle August 1, 2009 – April 9, 2013

• 73 activated studies
• 11,624 participants enrolled on studies
• 11,279 participants enrolled on Contact Registry
• 130 trainees
• 293 journal articles
• 61 conference presentations
• 50 books and book chapters
• 19 posters
<table>
<thead>
<tr>
<th>Protocol</th>
<th>Pharmaceutical Company</th>
<th>Type of support</th>
<th>Protocol Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCDC5102</td>
<td>Ucyclyd Pharma, Inc.</td>
<td>Drug</td>
<td>Closed to Accrual</td>
</tr>
<tr>
<td>UCDC5105</td>
<td>Orphan Europe</td>
<td>Drug</td>
<td>Pending implementation</td>
</tr>
<tr>
<td>UCDC5111</td>
<td>Orphan Europe</td>
<td>Full funding</td>
<td>Active</td>
</tr>
<tr>
<td>VCRC5522</td>
<td>Bristol-Myers Squibb</td>
<td>Supplemental funding and drug</td>
<td>Closed to accrual</td>
</tr>
<tr>
<td>VCRC5523</td>
<td>Bristol-Myers Squibb</td>
<td>Supplemental funding and drug</td>
<td>Active</td>
</tr>
<tr>
<td>VCRC5524</td>
<td>Office of Orphan Products Development</td>
<td>Full funding and drug</td>
<td>Pending implementation</td>
</tr>
<tr>
<td>VCRC5525</td>
<td>Roche, Genentech</td>
<td>Supplemental funding and drug</td>
<td>Pending implementation</td>
</tr>
<tr>
<td>VCRC5527</td>
<td>Bristol-Myers Squibb</td>
<td>Full funding and drug</td>
<td>Pending implementation</td>
</tr>
<tr>
<td>ARD6105</td>
<td>Baxter</td>
<td>Drug (IVIG)</td>
<td>Active</td>
</tr>
<tr>
<td>cGVHD6502</td>
<td>Novartis Corporation, Genentech</td>
<td>Drug</td>
<td>Active</td>
</tr>
<tr>
<td>cGVHD6503</td>
<td>GlaxoSmithKline Merck &amp; Co., Inc.</td>
<td>Drug</td>
<td>Active</td>
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<tr>
<td>LDN6703</td>
<td>Genzyme Corporation, Shire HGT</td>
<td>Supplemental funding</td>
<td>Active</td>
</tr>
<tr>
<td>LDN6707</td>
<td>Shire HGT</td>
<td>Supplemental funding</td>
<td>Active</td>
</tr>
<tr>
<td>LDN6708</td>
<td>Genzyme Corporation</td>
<td>Supplemental funding</td>
<td>Active</td>
</tr>
<tr>
<td>LDN6709</td>
<td>Genzyme Corporation</td>
<td>Funding for processing of whole blood sample, skin fibroblasts and mutation analysis</td>
<td>Active</td>
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<tr>
<td>LDN6711</td>
<td>Amicus Therapeutics, Shire HGT, Genzyme Corporation</td>
<td>Supplemental funding</td>
<td>Pending implementation</td>
</tr>
<tr>
<td>LDN6714</td>
<td>BioMarin Pharmaceutical, Inc.</td>
<td>Supplemental funding (vials of Aldurazyme from commercial source)</td>
<td>Active</td>
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<tr>
<td>NEPTUNE6803</td>
<td>Genentech</td>
<td>Drug</td>
<td>Pending implementation</td>
</tr>
<tr>
<td>NEPTUNE6804</td>
<td>Genentech</td>
<td>Full Funding &amp; drug</td>
<td>Active</td>
</tr>
</tbody>
</table>
## Contact Registry Protocols

<table>
<thead>
<tr>
<th>RDCRN #</th>
<th>Title</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCRC 5531</td>
<td>Reproductive Health of Men and Women with Vasculitis*</td>
<td>Closed to Accrual (N = 467) Accrual goal met in 2 mos.</td>
</tr>
<tr>
<td>VCRC 5533</td>
<td>Illness Perceptions, Fatigue, and Function in Systemic Vasculitis† (The VCRC Vasculitis Perception (VIP) Study)</td>
<td>Closed to Accrual (N = 707) Accrual goal met in 2 mos.</td>
</tr>
<tr>
<td>INC 6604</td>
<td>Development and Validation of a Disability Severity Index for Charcot-Marie-Tooth Disease (CMT)</td>
<td>Closed to Accrual (N = 249) Accrual goal met in 4 mos.</td>
</tr>
<tr>
<td>VCRC 5534</td>
<td>Educational Needs of Patients with Systemic Vasculitis - An International Study</td>
<td>Closed to Accrual (N = 386) Accrual goal met in 2 mos.</td>
</tr>
<tr>
<td>INC 6606</td>
<td>An Analysis of the Symptomatic Domains Most Relevant to Charcot Marie Tooth Neuropathy (CMT) Patients</td>
<td>Recruiting (opened 07/17/12) N = 357 as of 04/03/13</td>
</tr>
<tr>
<td>NEPTUNE 6802</td>
<td>Assessment of Educational Experience for Patients with Newly Diagnosed Nephrotic Syndrome</td>
<td>Recruiting (opened 01/03/13) N = 186 as of 04/03/13</td>
</tr>
</tbody>
</table>

### Abstracts:


Why RDCRN is successful

• Funding for Rare Disease Research
• Collaboration with Patient Advocacy Groups
• Common Infrastructure
• Rare Diseases Researcher Expertise and Support
• Mentoring of Next Generation of Researchers
• Coordinating Center Web Tools and Expertise
  – Contact Registry
  – eCRFs, Randomization, Treatment Assignment, etc.
  – Statistical Analysis expertise
  – IND submission expertise
  – Facilitating DSMB review
  – Audit program
New Treatments

DMCC and the Rare Lung Disease Consortium

Treatment of Idiopathic Pulmonary Fibrosis with Losartan: A Pilot Project

Marisa Coutulis · Brent W. Kinder · Ping Xu · Margaret Gross-King · Jeffrey Krieger · Ralph J. Purns

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Abstract

Background: Idiopathic pulmonary fibrosis is a progressive interstitial lung disease with no current effective therapy. Treatment has focused on antifibrotic agents to stop proliferation of fibroblasts and collagen deposition in the lung. We present the first clinical trial data on the use of losartan, an antifibrotic agent, to treat idiopathic pulmonary fibrosis. The primary objective was to evaluate the effect of losartan on progression of idiopathic pulmonary fibrosis measured by the change in percentage of predicted forced vital capacity (%FVC) after 12 months. Secondary outcomes included the change in forced expiratory volume at 1 second, diffusing capacity of carbon monoxide, 6-minute walk test distance, and baseline transplantation dyspnea index.

Methods: Patients with idiopathic pulmonary fibrosis and a baseline %FVC of ≥50% were treated with losartan 50 mg by mouth daily for 12 months. Pulmonary function testing, 6-minute walk, and breathlessness indices were measured every 3 months.

Results: Twenty participants with idiopathic pulmonary fibrosis were enrolled and 17 patients were evaluable for response. Twelve patients had a stable or improved %FVC at study month 12. Similar findings were observed in secondary end-point measures, including 58.71, and 85.0% of patients with stable or improved forced expiratory volume at 1 second, diffusing capacity for carbon monoxide, and 6-minute walk test distance, respectively. No treatment-related adverse events that resulted in early study discontinuation were reported.

Conclusions: Losartan stabilized lung function in patients with idiopathic pulmonary fibrosis over 12 months. Losartan is a promising agent for the treatment of idiopathic pulmonary fibrosis and has a low toxicity profile.

Keywords: Pulmonary fibrosis · Angiotensin receptor blocker · Forced vital capacity · Dyspnea · Six-minute walk test

Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive lung disorder with an identifiable cause or proven effective treatment [1]. Even though IPF is considered rare, it is the most common idiopathic interstitial lung disease and has both high morbidity and mortality. The median survival of patients with IPF is 2–4 years, which has not changed over the past decade [2, 3]. There is considerable evidence that angiotensin II (ANG II) is involved in multiple models of fibrosis. Angiotensin II is known to activate the angiotensin II receptor, inducing transforming growth factor expression [4, 5], which stimulates lung fibroblast proliferation and lung procollagen production. Losartan’s ability to alleviate fibrosis by reducing the expression of

Lung
DOI 10.1007/s00132-012-3485-z
New Treatments

Urea Cycle Disorders Consortium

N-carbamylglutamate Augments Ureagenesis and Reduces Ammonia and Glutamine in Propionic Acidemia
Nicholas Ah Mew, Robert McCarter, Yevgeny Daikhin, Itzhak Nissim, Marc Yudkoff and Mendel Tuchman
Pediatrics 2010;126:e208; originally published online June 21, 2010;
DOI: 10.1542/peds.2010-0008
Efficacy and Safety of Sirolimus in Lymphangioleiomyomatosis

Francis X. McCormack, M.D., Yoshikazu Inoue, M.D., Ph.D., Joel Moss, M.D., Ph.D., Lianne G. Singer, M.D., Charlie Strange, M.D., Koh Nakata, M.D., Ph.D., Alan F. Barker, M.D., Jeffrey T. Chapman, M.D., Mark L. Brantly, M.D., James M. Stocks, M.D., Kevin K. Brown, M.D., Joseph P. Lynch, III, M.D., Hilary J. Goldberg, M.D., Lisa R. Young, M.D., Brent W. Kinder, M.D., Gregory P. Downey, M.D., Eugene J. Sullivan, M.D., Thomas V. Colby, M.D., Roy T. McKay, Ph.D., Marsha M. Cohen, M.D., Leslie Korbee, B.S., Angelo M. Taveira-DaSilva, M.D., Ph.D., Hye-Seung Lee, Ph.D., Jeffrey P. Krischer, Ph.D., and Bruce C. Trapnell, M.D., for the National Institutes of Health Rare Lung Diseases Consortium and the MILES Trial Group*
Mexiletine for Symptoms and Signs of Myotonia in Nondystrophic Myotonia
A Randomized Controlled Trial

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Richard J. Barohn, MD
Michael G. Hanna, FRCP
for the Consortium for Clinical Investigation of Neurologic Channelopathies

Context: Nondystrophic myotonias (NDMs) are rare diseases caused by mutations in skeletal muscle ion channels. Patients experience delayed muscle relaxation causing functionally limiting stiffness and pain. Mexiletine-induced sodium channel blockade reduced myotonia in small studies; however, as is common in rare diseases, larger studies of safety and efficacy have not previously been considered feasible.

Objective: To determine the effects of mexiletine for symptoms and signs of myotonia in patients with NDMs.

Design, Setting, and Participants: A randomized, double-blind, placebo-controlled 2-period crossover study at 7 neuromuscular referral centers in 4 countries of 59 patients with NDMs conducted between December 23, 2008, and March 30, 2011, as part of the National Institutes of Health-funded Rare Disease Clinical Research Network.

Intervention: Oral 200-mg mexiletine or placebo capsules 3 times daily for 4 weeks, followed by the opposite intervention for 4 weeks, with 1-week washout in between.

Main Outcome Measures: Patient-reported severity score of stiffness recorded on an interactive voice response (IVR) diary (scale of 1 = minimal to 9 = worst ever experienced). Secondary end points included IVR-reported changes in pain, weakness, and tiredness, clinical myotonia assessment; quantitative measure of handgrip myotonia; and Individualized Neuromuscular Quality of Life summary quality of life score (INQOL-QOL, percentage of maximal detrimental impact).

Results: Mexiletine significantly improved patient-reported severity score stiffness on the IVR diary. Because of a statistically significant interaction between treatment and intervention period, results were analyzed separately. During placebo, mexiletine significantly improved patient-reported stiffness severity (IVR mean difference, 1.75; 95% CI, 0.47-2.94; P = .01). During mexiletine, placebo significantly improved patient-reported stiffness severity (IVR mean difference, 1.03; 95% CI, 0.00-2.05; P = .05). Significant improvements occurred in pain, weakness, and tiredness scores.

New Treatments
Consortium for Clinical Investigation of Neurologic Channelopathies
New Treatments

Inhaled Granulocyte/Macrophage–Colony Stimulating Factor as Therapy for Pulmonary Alveolar Proteinosis

Rare Lung Disease Consortia
Seroreactivity to LGL leukemia-specific epitopes in aplastic anemia, myelodysplastic syndrome and paroxysmal nocturnal hemoglobinuria: Results of a bone marrow failure consortium study

Thank you!

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