The Transformation of Clinical Research in Vasculitis Through the Rare Diseases Clinical Research Network

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Vasculitis is a family of rare, complex, severe/life-threatening, multi-organ system diseases that involve inflammation of blood vessels.
The Vasculitides

- Immune Complex Small Vessel Vasculitis
  - Cryoglobulinemic Vasculitis
  - IgA Vasculitis (Henoch-Schönlein)
  - Hypocomplementemic Urticarial Vasculitis
    - (Anti-C1q Vasculitis)
- Medium Vessel Vasculitis
  - Polyarteritis Nodosa
  - Kawasaki Disease
- Anti-GBM Disease
- ANCA-Associated Small Vessel Vasculitis
  - Microscopic Polyangiitis
  - Granulomatosis with Polyangiitis
    - (Wegener’s)
  - Eosinophilic Granulomatosis with Polyangiitis
    - (Churg-Strauss)
- Large Vessel Vasculitis
  - Takayasu Arteritis
  - Giant Cell Arteritis
The Vasculitis Clinical Research Consortium

The VCRC is an international, multicenter research infrastructure for conducting clinical and translational investigation in various types of vasculitis.
The VCRC has transformed clinical research in vasculitis

The development and growth of the VCRC is completely the result of the development of the RDCRN
Vasculitis Clinical Research Consortium

• Founding member of the NIH RDCRN
• Funding:
  – Consecutive 5-year U54 grants ($6M each)
    • Now in cycle 3 (year 11)
  – Several additional grants for specific projects
• PI: Peter A. Merkel, MD, MPH
• Consortium Coordinating Center: University of Pennsylvania
• Steering Committee: site PIs, patients, DMCC
The VCRC Diseases

Primary Diseases Under Study

- Takayasu’s Arteritis
- Giant Cell Arteritis
- Polyarteritis Nodosa
- Granulomatosis with Polyangiitis (Wegener’s)
- Microscopic Polyangiitis
- Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)

Additional Diseases for Registry

- Behçet's Disease
- Cryoglobulinemic Vasculitis
- CNS Vasculitis
- Hypocomplementemic Urticarial Vasculitis
- IgA Vasculitis (HSP)
- Undifferentiated Vasculitis
Vasculitis Clinical Research Consortium
North American Clinical Sites

Many additional VCRC partner sites in EU, Asia, Australia
## VCRC Protocols

### Clinical Cohorts and Biospecimens

**Repository: Biomarker Studies**

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VCRC Longitudinal Studies

• Studies of GCA, TAK, PAN, GPA, MPA, EGPA

• Comprehensive clinical data linked to collection of serum, plasma, urine, and DNA
  – Biomarker development
  – Genetic studies
  – Clinical epidemiology/outcomes

• Patients are seen quarterly (2/3) or annually (1/3)

• Long-term follow-up (currently up to 8 years)

• Electronic data entry with centralized data and specimen repositories
VCRC Vasculitis Biorepository

• All VCRC specimens are stored in one repository at Penn
  ▪ >48,000 samples: from >2,000 subjects at >11,000 visits (290,000 vials)
  ▪ DNA, serum, plasma, urine, PBMCs
  ▪ 6 forms of vasculitis
  ▪ All specimens linked to comprehensive clinical/phenotypic data
  ▪ Includes longitudinal samples and data on most patients

• Largest such collection in the world

• Utilized for many genetic, biomarker, clinical, other projects

• Potential for study-specific additions
  ▪ Tissue
  ▪ Cell sorting
Examples of VCRC Biomarker Studies

- **Markers of vascular injury and angiogenesis**
  - *Angiopoietin-2* in AAV with P. Kümpers and M. Haubitz
  - *MMPs, Selectins, etc.* with R. Snyder

- **Chemokines, cytokines, tissue injury and repair**
  - *28 markers* on custom array with K. Johnson
  - MIF with R. Bucala and A. Sreih

- **Platelet-endothelial interaction and thrombosis**
  - Marker of vascular inflammation with J. Freedman

- **IgA ANCA in AAV**
  - *PR3 and MPO,* with R. Kimberly

- **Eotaxin-3 and CCL17/TARC in EGPA (Churg-Strauss)**
  - *With J. Zwerina*

- **Targets of anti-endothelial cell Abs in GCA and Takayasu’s**
  - With R. Karasawa

- **Markers of T cell activation**
  - With P. Heeger

- **Many other studies in various stages**
Sample of VCRC Genetic Studies

• Genome-Wide Association Studies
  – *GPA/MPA GWAS validation study (700 subjects) → A&R 2013
  – New GWAS with 2500 patients with GPA, MPA, or EGPA (CSS)
    – Ongoing; well-positioned for large GWAS with EU validation set
  – *Validation study of TAK GWAS → Am J Hum Genetics 2013
  – Exploratory small GWAS of EGPA (CSS)
  – Validation cohort for GWAS of GCA with EU group

• Candidate-gene studies in GCA, TAK, PAN, GPA, MPA, CSS
  – MIF (Bucala-Yale)
  – *IgA and IgG FcR functional polymorphisms (Kimberly-UAb)
  – *Susceptibility gene in African-Americans with AAV (Preston-UNC)
  – Complement genes (Hageman-Utah)
  – Genes associated with GCA (Monach-BU)
  – Novel genes with PAN-like disease (Kastner-NHGRI)

• Exome sequencing studies
  – Linked to the AAV GWAS studies (Kim-WashU)

• Epigenetic studies
  – Epigenetics of AVV (Chung-UCSF)
Sample of VCRC Clinical Data Analyses

- *COMEX: Comparisons of BVASs(3)
- *Physician ranking of outcomes (Seo)
- *Patient-reported burdens of disease (Heryln)
- *Association between physical exams and MRI in LVV (GCA and TAK) (Grayson)
- *Cluster analysis of patterns of arterial involvement in GCA and TAK (Grayson)
- Patterns and predictors of flares in GCA (Kermani)
- *Utility of SF-36 in AAV (Tomasson)
- Activity and damage assessment in LVV (Sreih/Kermani)
- Characteristics of patients in cohorts vs. trials (Pagnoux)
- Patterns of progression in vasculitides (Grayson)
- *Mapping ICF domains to vasculitis (Milman)
- IBD and cardiac disease in vasculitis (Pagnoux)
- Several others in preparation
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VCRC Patient Contact Registry

- Patients with vasculitis can register with the VCRC to allow for:
  - Future contact regarding studies
  - Updates on research

- Helps create a group “ready to go”
  Internet-based; international

- ~4000 patients already registered

www.RareDiseasesNetwork.org/vcrc
Roles of the VCRC

Patient Contact Registry

- Promotion of PAG Activities
- E-Newsletter
- Portal for Online Research
- Recruitment
- Direct links to VCRC studies
- Contact information
- Event notification
- Links to PAG sites
- Study updates
- Educational information
- Dissemination of study results
- Clinical epidemiology
- Surveys
- Outcome measures
- Clinical trials
- Contact information

Join the VCRC Contact Registry

VASCULITIS CLINICAL RESEARCH CONSORTIUM
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PCORnet: The Vasculitis Patient-Powered Research Network (V-PPRN)
PCORnet: The National Patient-Centered Clinical Research Network

Improving Our National Infrastructure to Conduct Comparative Effectiveness Research

The Patient-Centered Outcomes Research Institute (PCORI) is supporting the development of PCORnet, the National Patient-Centered Clinical Research Network, to create a large, highly representative...
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VCRC-NIAMS DSMB

• NIAMS recognized need for Consortium-specific DSMB with expertise in vasculitis and independence from investigators

• The NIAMS-VCRC DSMB now oversees all VCRC projects
  – Efficient review and approval of new studies given familiarity with diseases and investigators
  – Shorter start-up since DSMB formed and processes in place
  – Independence well maintained
  – Institute retains control/oversight

• Model for RDCRN
  – High level of satisfaction by program officials, DSMB members, and investigators
  – Acceptance and appreciation by industry/funders
Use of an IRB of Record within the VCRC
IRB of Record

• One institution takes primary responsibility for IRB oversight, approval, review
• All other institutions defer to IRB of Record
• Markedly reduces site times, costs
• Growing approach in US; academic centers adapt slowly but are changing
• This SHOULD & WILL happen and be the norm
• Especially important for work in rare diseases
• NIH is moving towards this as model for clinical research
IRB of Record Within the VCRC

• The University of Pennsylvania has a progressive IRB willing to take the lead as the IRB of Record
• NIH *strongly* urged this to happen
• Currently in place in three VCRC clinical trials
• VCRC-Penn now has substantial experience with this process
• There a learning curve:
  – Host institution
  – Participating sites
  – Investigators/study staff
VCRC-VF Vasculitis Fellowship Program in Clinical Investigation
VCRC-VF Fellowship Goals

• To familiarize trainees with the investigative issues, biology, and clinical presentations of different types of vasculitis

• To teach trainees how to successfully undertake translational/clinical research
VCRC-VF Fellowship Structure

- One or two-year clinical research fellowship
- Fellow/Mentor a VCRC sites
- Clinical work limited to 20% effort
- Graduate coursework strongly encouraged
- Co-funded by the Vasculitis Foundation
- VCRC-VF pays 50% of salary; site pays 50%
- Fellow selected by committee that includes VF rep
Success of the VCRC-VF Fellowship

- All fellows remain in academic medicine and study vasculitis
- All fellows continue to see patients with vasculitis
- Former Fellows are now funded and leading on studies
- Fellows have opened new vasculitis centers
- This may be the best thing the Consortium does!
Central Role of CTSA in VCRC

- All US VCRC sites with CTSA use these resources for VCRC studies
  - Exam rooms/time
  - Treatment administration
  - Skilled research nursing
  - Specimen collection and processing
  - Core facilities

- Key resource for research in rare diseases

- Economics becoming challenging
The DMCC is a crucial component to the RDCRN

- Expertise in study design/biostatistics
- Experience in large multi-center, international studies
- Extremely efficient, scalable, high-quality trial infrastructure

Computerized data entry ♦ AE reporting system
Drug distribution capabilities ♦ Specimen tracking
Sophisticated data storage ♦ Analysis of “Big Data”
Data and trial monitoring ♦ Regulatory expertise
Study personnel training ♦ Website design and hosting

The RDCRN DMCC reduces costs, increases productivity, and improves the quality of the science
Grants Awarded/Related to the VCRC

Clinical Trials
• AGATA Trial Contract (NIAMS)
• R01: PEXIVAS (FDA)
• R01: Novel Methods for Clinical Trials (NHLBI)
• Genentech IST Grant for RITAZAREM
• Bristol-Myers Squibb IST Grant for ABROGATE

Training and Education
• Career Development Awards
  o NIAMS Ks: Dr. Seo, Dr. Chung
  o AF CDA: Dr. Monach
  o ACR/RRF: Drs. Grayson, Sreih, and Tomasson
• R13 Meeting Grants (2) 2006 (NCRR) and 2009 (NINDS)

Clinical Outcomes and Outcome Measurement Development
• Institutional awards to VCRC Fellows: Drs. Kermani, Koening, and Mahr
• U01 Outcomes Projects (NIAMS)
• R01: PROMIS (NIAMS)
• PCORI Pilot Grant
• PCORI PCORnet V-PPRN

Biomarker and Genetics Program
• P60 MCRC Biomarker Studies (NIAMS)
• Pilot Project Grant (NCRR)
• RC1: Biomarkers (NIAMS)
• 2 Canadian grant for biomarkers
• 1 Institutional grant

Patient Contact Registry Program
• RC1: Contact Registry
• VF Project Grant: VCRC RPHQ/VReg
The VCRC has successfully created a flexible and sustainable infrastructure for collaborative clinical investigation in vasculitis and conduct of novel research studies and designs.

The VCRC is now the world’s leading clinical research program in vasculitis.
Transformative Components of the VCRC

• Core infrastructure
  – No need to re-invent the wheel each time
  – Institutional and personal memory
  – Data Management and Coordinating Center (DMCC)

• Recycle resources and concepts

• NIAMS-VCRC DSMB
  – Markedly improves efficiency & quality of protection

• IRB of Record:
  – Cost and time-effective and improves protection

• “Brand” awareness

• Academia-NIH-Industry collaborations

• Meaningful patient engagement
  – Support → consulting → co-investigating/collaboration

• Integration of training of new investigators

• Promotes broader, cross-cutting, and ambitious programs
The Teammates That Made It Happen

NIAMS

VF

RDCRN DMCC

ORDR

NCRR/NCATS

VASCU LISIS CL IN ICA L RESEARCH CONSORTIUM
Questions/Comments