ITN Achieves Scientific Manuscript First - Provides Open, Interactive Access to Clinical Trial Data

Immune Tolerance Network (ITN) researchers published data of their “Rituximab for the Treatment of Wegener’s Granulomatosis and Microscopic Polyangiitis (RAVE)” clinical trial using ITN TrialShare, a clinical trial data and analysis portal that provides open, unprecedented access to clinical trial data, analyses and specimens.

WA, Seattle (July 26, 2013) – In an article reporting the 18-month results of the ITN’s RAVE clinical trial, published August 1st in the New England Journal of Medicine, the ITN is providing unfettered access to the underlying clinical data and analysis code via the new clinical trials research portal, ITN TrialShare (itntrialshare.org). TrialShare is a significant advance in data sharing and transparency, allowing for collaborative hypothesis generation and specimen sharing between the ITN and the broader scientific community. TrialShare gives researchers the ability to access raw study data, confirm published conclusions and interactively perform their own exploratory analyses using this data.

“Direct access to raw clinical trial data will change the landscape of collaborative research” said Peter C. Grayson, MD, MSc of Boston University Medical Center, a collaborator with the ITN. “TrialShare creates unfettered opportunities to explore and understand the intricacies of clinical trial data. Better understanding of primary data leads to better downstream applications of that data.”

The FDA has announced that it intends to consider making de-identified and masked subject level data widely available to improve the efficiency and effectiveness of medical product development, recognizing that external experts should become actively engaged in the research. ITN TrialShare was created precisely to address this need, enabling researchers to share the results of the clinical trial data in an open and transparent manner, while protecting the privacy and anonymity of study participants by fully de-identifying the data. TrialShare provides tools that allow external researchers to confirm results while providing access to the underlying data, ensuring that nothing is missed or overlooked. TrialShare also provides access to the ITN specimen repository catalog, allowing users external to the trial to request specimens for follow-up experiments based on the data and available samples.

“TrialShare allows researchers from around the world to have direct access to ITN’s clinical trial data” said Gerald T. Nepom, MD, PhD, director of the ITN. “This will enhance scientific collaboration and greatly speed the sharing of the results of our studies.”

In recognition of the system’s approach to analytic transparency, ITN Trial Share was recently awarded “Best Practices Award – Honorable Mention” at the April, 2013 Bio-IT World Conference in Boston. The Bio-IT World’s Best Practices Awards “recognize organizations for their outstanding innovations and excellence in the use of technologies that advance biomedical and translational research, and clinical trials.” (http://www.bio-itworld.com/2013/4/10/best-practices-winners.html).
With the addition to TrialShare of the data from today’s publication, ITN TrialShare currently has data associated with six published manuscripts available to the public in the therapeutic areas of transplant, allergy, auto-immunity and diabetes. ITN will make the underlying data from all published studies, regardless of outcome, available through TrialShare. ITN TrialShare uses the open source LabKey server software. TrialShare can be accessed at ITNTrialShare.org.

About The Immune Tolerance Network

The Immune Tolerance Network (ITN) is a research consortium sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health along with additional support from NIDDK and JDRF. The ITN develops and conducts clinical and mechanistic studies of immune tolerance therapies designed to prevent disease-causing immune responses, without compromising the natural protective properties of the immune system. Visit www.immunetolerance.org for more information.

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ITN TrialShare is an interactive data sharing and analysis platform created by the Immune Tolerance Network (ITN) to provide access to data, analyses and analysis tools, and samples from ITN clinical trials of novel tolerance therapies in autoimmune diseases, organ transplantation and allergy & asthma.

Users can view and download de-identified patient-level, longitudinal clinical data linked with wide-ranging laboratory assay results such as flow cytometry, gene expression and immunohistochemistry.

Gene Signatures
Review and re-analyze gene expression data for biomarker studies

Clinical Outcomes
Review and re-run clinical analyses using various subsets of data

Imaging
Review biopsy data for transplantation studies
Many of the things you can do in TrialShare start with a dataset. You can view and download datasets, and create your own views and charts.

To view a dataset:
1. Choose a Study and click “Data & Reports”
2. Scroll to “Data Sets and Views” and click a dataset

To create a chart:
1. Click "CHARTS"
2. Click the type of graph you want to create

To filter a dataset:
1. Click a column header
2. Select “Filter”
3. Select the values you want or click “Choose Filters”
4. Type the filters you want

To download a dataset:
1. Click “Export” in the dataset header
2. Choose an export format
3. Click the button below your selection
4. Click “Export” again to collapse the panel

Information in TrialShare is organized by Study
A Study contains protocol information, datasets and reports. It may also contain participant records, specimen inventory, raw data files and other assets.
Clinical Trial Transparency:
The movement towards improved clinical trial transparency is steadily growing, driven forward by the scientific and ethical concerns raised by the significant underreporting of clinical trial results; but true transparency requires more than simple registration and publication of select clinical trial data.

The FDA has announced that it intends to consider making public de-identified and masked subject level data to improve the efficiency and effectiveness of medical product development recognizing that external experts should become actively engaged in the research.1

However, the complexity and heterogeneity of clinical trial data have created substantial technological barriers to this vision. The ITN TrialShare platform marks a revolutionary step forward in fulfilling the vision of true clinical trial transparency.

ITN TrialShare:
ITN TrialShare is a clinical research data portal and analysis platform that permits the sharing of detailed data, annotations and analyses from clinical trials and provides advanced interactive tools for its reuse and analysis. Developed by the Immune Tolerance Network (ITN), a project of the National Institute of Allergy & Infectious Diseases, TrialShare provides a comprehensive set of features and tools that open the door for a new era in clinical trial transparency. The system:

- Enables sharing of complex clinical trial and research assay data in simple and easy-to-use formats, allowing custom subset definition and data export in a variety of formats
- Provides access to patient-level data including longitudinal views of individual and user defined groups, pathology images, gene expression data, visit histories and more
- Allows users to re-run and revise analyses using stored statistical codebases
- Brings interactive advanced visualizations from trial data to the desktop with web-based graphical analysis tools
- Creates interactive figures for manuscript publication that give reviewers, editors and readers the ability to delve deeper into the data and accompanying analyses

As part of the ITN’s commitment to full disclosure, the ITN has, to date, released over 1000 datasets, reports, and interactive figures with underlying statistical code from 6 of its clinical trials. This includes the statistical code behind analyses of published flow cytometry, gene expression microarray, and cell based assay data. In addition, information on 270,000 bio-repository samples is also available. In the past 4 months, over 150 public user accounts were created leading to over 30,000 hits by individuals downloading or reviewing de-identified data.

ITN Trial Share was recently awarded “Best Practices Award – Honorable Mention” at the April, 2013 Bio-IT World Conference in Boston. Of the 34 projects evaluated, ITN received one of two honorable mentions. The Bio-IT World’s Best Practices Awards “recognize organizations for their outstanding innovations and excellence in the use of technologies and novel business strategies that will advance biomedical and translational research, drug development, and/or clinical trials.”

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The Immune Tolerance Network (ITN), headquartered at the Benaroya Research Institute in Seattle, WA, is an international clinical research consortium sponsored by NIAID, part of the National Institutes of Health. Our mission is to accelerate the clinical development of immune tolerance therapies in solid organ transplantation, autoimmune disease and asthma & allergy.

Immune tolerance therapies reprogram the immune system in a highly specific manner so that disease-causing immune responses are stopped while maintaining the immune system’s ability to combat pathogen infection. Short-term tolerance therapies carry low risks of serious complications due to their specific nature and, unlike currently available immunosuppressive treatments that must be taken for life, avoid serious complications of harmful infections and certain types of cancer.

ITN by the Numbers:

- Active in 10 countries with ITN sites or members
- 48 clinical trials - 9 Allergy trials; 23 Autoimmunity trials; 16 Transplant trials
- 178 clinical sites and investigators at leading academic hospitals worldwide
- 3000+ patients enrolled in ITN clinical trials
- 100+ tolerant patients off of all immunosuppression to date
- 16 core labs performing standardized routine and specialized assays
- 68 Full time employees plus a steering committee of 30 physicians and scientists
- 108 peer-reviewed publications in top-tier biomedical journals
- 177 meeting abstracts presented at national and international meetings
- 375,000 clinical specimens in the ITN repository

Key Accomplishments

- Successfully completed the world’s first multicenter clinical trial of a standardized protocol for islet cell transplantation for type 1 diabetes [New Engl J Med, 2006]
- Established proof-of-concept that a novel anti-CD3 drug could preserve beta cell function in recently diagnosed type 1 diabetes patients for over 5 years [Clin Immunol, 2009]
- Discovered a unique genetic signature in transplant patients that may indicate a propensity for tolerance [J Clin Invest, 2010]
- Showed that up to 60% of selected pediatric liver transplant recipients may safely discontinue all immunosuppression in a closely supervised manner, without transplant rejection [JAMA, 2012]
- Demonstrated that combined bone marrow and kidney transplant can induce long-term tolerance with no need for ongoing immunosuppression in HLA-mismatched recipients [New Engl J Med, 2008]
- Currently performing the definitive study of childhood peanut allergy prevention, with results due FALL, 2014

www.immunetolerance.org
Rituximab Therapy Effective for ANCA-associated Vasculitis

Immune Tolerance Network researchers demonstrate rituximab is as effective as the standard treatment protocol in ANCA-associated vasculitis.

WA, Seattle (July 26th, 2013) – In an article published today in the New England Journal of Medicine, Immune Tolerance Network (ITN) researchers demonstrated that a single course of rituximab therapy (anti-CD20; Rituxan, Genentech, Inc.) is as effective as the current standard of care regimen of drugs for remission induction and maintenance in patients with ANCA-associated Vasculitis (AAV). AAV is an autoimmune disease marked by the presence of antibodies that attack neutrophils and cause inflammation of the blood vessels, leading to organ damage and sometimes death. The standard of care for this disease was cyclophosphamide, a potent immunosuppressant that although effective is very toxic when used long-term. Rituximab has a shorter and simpler treatment course compared to standard therapy, thus offering significant treatment advancement for patients with AAV.

The RAVE study is a 197-patient randomized, double-blind, placebo-controlled trial comparing rituximab against cyclophosphamide for remission induction in patients with severe AAV. This clinical trial is led by John Stone, MD (Massachusetts General Hospital) and Ulrich Specks, MD (Mayo Clinic), and is sponsored by the ITN, a clinical trial network funded by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health. The FDA approved a label extension for rituximab for use in AAV after the initial 6-month results of the RAVE study demonstrated that rituximab in combination with glucocorticoids was non-inferior to cyclophosphamide in combination with glucocorticoids for inducing complete remission in patients with severe AAV (reported in the New England Journal of Medicine in 2010; www.nejm.org/doi/full/10.1056/NEJMoa0909905). This represented the first approved therapy for AAV in over 40 years. Today’s publication reports safety and relapse rates among the two treatment groups out to month 18. Patients in the rituximab arm received only one, short course of therapy over 4 weeks, and those in remission received only placebo therapy through month 18. Alternately, patients in the standard therapy arm received 3-6 months of cyclophosphamide followed by azathioprine through the length of the study. Patients who achieved remission had glucocorticoids discontinued before month 6 and did not take any glucocorticoids through month 18 if they remained in remission.

At 18 months, 39% of patients in the rituximab arm were relapse-free (n=39), compared to 33% in the standard therapy arm (n=32). There were no significant differences in overall adverse events between the two groups, although there were fewer cases of pneumonia and leukopenia in the rituximab arm. These results suggest that a short course of rituximab (four once weekly infusion) is as effective for the induction and maintenance of remission in severe AAV patients as continuous treatment over 18 months with standard immunosuppressive drugs that require ongoing monitoring for toxicities.
“The RAVE study is remarkable for several reasons”, said Ulrich Specks. “First, its results have provided patients who suffer from these chronically relapsing diseases with access to a very effective alternative to cyclophosphamide to induce remission. Second, the study has shown that a short course of 4 infusions of rituximab is as effective as 18 months of ongoing daily oral therapy with immunosuppressive drugs that require frequent blood test monitoring to assure their safe use. Third, the RAVE study is a model for successful partnerships of federal funding agencies, federally funded research organizations and industry for the study of rare diseases. Last not least, today’s publication illustrates how complete transparency between published study analyses and all raw study data can be provided to the public”.

Data sets and statistical analyses from the RAVE study are available to the public through ITN TrialShare, www.ITNTrialShare.org, a new clinical trials research portal. This publication is the first to provide public access to the raw study data via direct links from the publication and its figures to the data sets in ITN TrialShare. This represents a big step forward in the general quest for complete transparency of all data accumulated during the conduct of clinical trials.

**About The Immune Tolerance Network**

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