CLINICAL RESEARCH ALLIANCE newsletter

CROHN'S & COLITIS FOUNDATION OF AMERICA

Clinical Research Alliance Meeting

Saturday December 15, 2012
12.30 pm – 2 pm
Location: Conference room 307
(room will be open at 12:00pm)

12.30-12.35
Update CRA
Hans Herfarth and Peter Higgins

12.35-12.50
Updates on CRA Projects

Update on MERIT-UC
Hans Herfarth

Update on PIANO
Uma Mahadevan

Update on PUCCINI
Bruce Sands

12.50-1.10
The Pediatric IBD Network: Studies and lessons to be learned
Subra Kugathasan and Lee Denson

1.10-1.20 Discussion

1.20-1.35
New perspectives: Phase 4 studies of drug safety involving FDA, industry and CRA.
Peter Higgins

1.35-1.50 Discussion

MERIT-UC (MEthotrexate Response In Treatment of UC)

BACKGROUND:

There are fewer therapeutic options for patients with active ulcerative colitis (UC) compared to patients with active Crohn's disease (CD) and we are facing a persistent unmet need for additional effective and affordable therapies for patients with UC. Methotrexate (MTX) 25 mg once weekly administered subcutaneously (sq) or intramuscularly (im) is an efficient therapy to induce and maintain steroid free remission in patients with CD. Only one small prospective placebo controlled trial investigating the oral administration of 12.5 mg MTX once weekly compared to placebo has been conducted. The results did not demonstrate superiority of MTX compared to placebo. We conducted a systematic literature research to identify published clinical efficacy data of MTX in patients with UC and found several retrospective and prospective case series demonstrating clinical efficacy of MTX, when the drug was administered in a comparable dose and similar route (im or sq) as in CD. The conflicting data of the only placebo controlled trial and the published clinical experience may be explained by the fact, that MTX has a known dose response curve as shown in patients with CD or rheumatoid arthritis and also has a significant lower bioavailability if applied orally especially in higher doses such as the one used in CD. We therefore hypothesize that MTX presents an effective therapy for patients with UC if administered in a similar fashion as in CD patients.

RELATED PUBLICATIONS:

Herfarth HH, Long MD, Isaacs KL; Methotrexate: Underused and Ignored? Dig Dis DOI: 10.1159/000342735, in press 2012

Herfarth HH, Osterman MT, Isaacs KL, Lewis JD, Sands BE; Efficacy of methotrexate in ulcerative colitis: Failure or promise. Inflamm Bowel Dis 2010;16:1421-30.

Chairman Clinical Research Alliance
Hans Herfarth, MD, PhD
hherf@med.unc.edu

Co-Chairman Clinical Research Alliance
Peter Higgins, MD, PhD, MPH
phiggins@med.umich.edu

Director of Collaborative Research Projects, Crohn's and Colitis Foundation of America
Tania Kamphaus, PhD
tnkamphaus@ccfa.org

CRA Administrative Assistant
Susan Jackson, MPA
susan_jackson@med.unc.edu

DECEMBER 2012 www.ccfacra.org

CLINICAL RESEARCH ALLIANCE
newsletter

MERIT-UC, Continued...

AIMS of MERIT-UC

MERIT-UC is a NIH funded multi-center prospective placebo controlled study to investigate the safety and efficacy of 25 mg MTX applied subcutaneously once weekly in patients with active UC, who are either steroid dependent or are intolerant or not responding to 5-ASA's or azathioprine/6-mercaptopurine therapy or have no response/ lost response to infliximab prior to the study inclusion.

The aims of the trial are:

1) To evaluate the safety and tolerability of 25 mg MTX applied sq once weekly over a time period of 48 weeks.
2) To evaluate the relapse-free survival of MTX maintenance therapy compared to placebo over a time period of 32 weeks.
3) To evaluate the efficacy of MTX over a time period of 16 weeks to induce steroid free remission.
4) To establish a DNA, plasma and serum library to enable the evaluation of clinical and pharmacogenomic models to predict the response to MTX therapy in patients with UC.

ACTIVE SITES IN MERIT-UC

Currently we have 27 active sites and 7 sites are preparing to join the consortium (if you want to see who is participating check the CRA website www.CCFACRA.org). We are still looking for new sites. If you are, or know of a site, that might be interested, please contact Hans Herfarth of MERIT-UC: hherf@med.unc.edu.

RECRUITMENT

So far we have screened 50 patients for the study and included 30 into the open label induction period. We hope to further increase screening and recruitment in the next few months.

Contact for MERIT-UC – Hans Herfarth, MD, PhD
hherf@med.unc.edu

PIANO: PREGNANCY IN INFLAMMATORY BOWEL DISEASE AND NEONATAL OUTCOMES

Objectives and Aims: Unchanged from original Proposal

Hypothesis: Women with IBD exposed to azathioprine/6-mp and anti-TNF therapies during pregnancy and conception have different pregnancy outcomes than women with IBD not exposed to these medications.

Primary Objective:

- Determine whether the rates of congenital malformations, spontaneous abortion, preterm birth and small for gestational age (SGA) infants in a prospective national sample of women from the United States with IBD exposed to azathioprine/6MP or anti-TNF therapy are greater than those among IBD-affected women not exposed to these medications
- Determine 4 year outcomes of infants born to mothers with IBD with respect to developmental delay, infections and other health related complications

Secondary Objectives:

- Determine whether the rate of any adverse pregnancy outcomes (defined below) in a prospective national sample of women from the United States with IBD differ with respect to exposure to azathioprine/6MP or anti-TNF therapy
- Determine factors that predict adverse pregnancy outcomes in a prospective national sample of women from the United States with IBD
- Determine rates of disease activity during pregnancy and the post-partum in a prospective national sample of women from the United States with IBD

CLINICAL RESEARCH ALLIANCE
newsletter

PIANO, Continued...

- Determine whether adverse outcomes are more common when the expectant mother has active IBD than when the expectant mother has quiescent IBD
- Determine the rate of neonatal complications (defined below) up to one year from birth in a prospective national sample of children born to women from the United States with IBD

Results

- This project received approval from the CCFA in late January of 2007. Institutional review board (IRB) approval was obtained from the University of California, San Francisco by July 2007.
- At this time 31 sites have received IRB approval and have been contracted to participate in this study
- As of October 26, 2012, 1087 patients have been enrolled in the registry
- 337 patients have enrolled in the PIANO extension
- Along with the data monitoring center at the University of North Carolina, case report forms have been continually upgraded as the various sites proceeded through the multiple questionnaires. A sophisticated website for data entry has been created that can be accessed on-line by each study site. We have created programs that send automated reminders to each site for when each individual patient questionnaire is due. We have had excellent compliance with less than 2% of the forms being delinquent
- Patients who have delivered are eligible for the extension with questionnaires at infant years 1, 2 ,3 and 4. In addition to maternal and infant health questionnaires, Ages and Stages developmental questionnaires are filled out as well.

Publications:

a. Abstract presented as an oral presentation at DDW in 2009, 2010, 2012

b. IMIBD Plenary Session presentation 2012

c. This study will generate multiple papers. All contributors will be on at least one publication from this.

d. Paper for PIANO in progress

2013 plans

a. Funding requested from CCFA SRA for a 3 year study to measure placental and breastmilk levels of anti-TNF at birth and correlate with infections. Also will capture data on newer medications approved for IBD

b. Funding requested for separate study to analyze B and T cell development based on drug exposure

Interim Analysis 5/12

a. 1000 women enrolled, 896 have delivered

b. Group A (azathioprine/6mp) n= 204; Group B (biologics) n = 291; Group AB (both) n= 75; Unexposed (to aza/biologics) n = 326

c. Overall minimal differences between Group A, B, AB and unexposed group, except:

   i. Increased risk of preterm birth Group AB: OR 1.83 (1.01-3.31)

   ii. No statistical increased risk of complications, infections, congenital anomalies based on medication exposure

Contact for PIANO- Uma Mahadevan, MD
uma.mahadevan@ucsf.edu

CLINICAL RESEARCH ALLIANCE
newsletter

PUCCINI: Prospective Cohort of Ulcerative Colitis and Crohn's Disease Patients Undergoing Surgery to Identify Risk Factors for Post-Operative INfection I

Hypothesis:

IBD patients exposed to anti-TNF therapies pre-operatively have a higher rate of post-operative infections within 30 days than patients not exposed to these medications.

Primary Objectives:

- Determine whether the rate of post-operative infection (surgical site infections and extra-abdominal infections) in a prospective multi-center sample of IBD patients undergoing abdominal surgery is greater in patients exposed to anti-TNF therapy than those unexposed to these medications.
- Determine whether anti-TNF exposure is an independent risk factor for post-operative infection in a multicenter prospective sample of IBD patients undergoing abdominal surgery.

Secondary Objectives:

- Determine if exposures to other IBD therapies including corticosteroids, antibiotics, thiopurines, methotrexate, cyclosporine, and natalizumab are associated with an increased rate of post-operative infection in a prospective multi-center sample of IBD patients undergoing abdominal surgery in the United States.
- Determine other risk factors that predict post-operative infection in a prospective multi-center sample of IBD patients undergoing abdominal surgery in the United States.
- Determine predictors of short term pouch specific complications in a prospective multi-center sample of IBD patients undergoing Ileal Pouch Anal Anastomosis (IPAA) in the United States.
- Determine predictors of non-infectious outcomes such as hospital re-admission, re-operation, thrombotic complication, and mortality in a prospective multi-center sample of IBD patients undergoing abdominal surgery in the United States

Status Update

- Pilot study sites (PI/Co-Investigator)
  - Cleveland Clinic Foundation (Bo Shen, Feza Remzi)
  - Massachussetts General Hospital (Vijay Yajnik, Liliana Bordeianou)
  - The Mount Sinai Hospital (Bruce Sands, Benjamin Cohen, Joel Bauer)
  - University of Michigan Hospital (Peter Higgins, Karin Hardiman)
  - University of North Carolina Hospitals (Hans Herfarth, Mark Koruda)
- Electronic CRFs created by UNC/Dartmouth from detailed study protocol.
- Patient recruitment began late September 2012. 53 patients enrolled as of October 22.
- Pilot site conference calls including research coordinators, IBD gastroenterologists, and IBD. surgeons have been taking place every 2 weeks since August. Calls have been used to modify enrollment strategies, trouble shoot electronic CRF forms, and prepare for larger grant submission.
- Letter of intent submitted for CCFA Senior Research Award

Contact for PUCCINI – Bruce Sands, MD
bruce.sands@mssm.edu

CLINICAL RESEARCH ALLIANCE newsletter

CURRENT CRA MEMBERS

Atlanta Gastroenterology Associates
5671 Peachtree Dunwoody Rd, Suite 600
Atlanta, GA 30342
Douglas C. Wolf, MD
m4desk@aol.com

Baylor College of Medicine
1709 Dryden St, Suite 800
Houston, TX 77030
Bincy Abraham, MD
bincya@Bcm.edu

Beth Israel Medical Center
Division of Digestive Diseases
10 Union Square East, Suite 2G
New York, NY 10003
David Hudesman, MD
DHudesma@chpnet.org

Boston Medical Center
Section of Gastroenterology
85 East Concord Street
Boston, MA 02115
Francis A. Farraye, MD, MSc
francis.farraye@bmc.org

Brigham and Women's Hospital
Gastroenterology Division
75 Francis Street ASBII
Boston, MA 02115
Sonia Friedman, MD
sfriedman1@partners.org

Carle Physicians Group
602 West University Ave
Urbana, IL 61801
Eugene Greenberg, MD
eugene.greenberg@carle.com

Cedars-Sinai
8635 W 3rd Street #960 W
Los Angeles, CA 90048
Gil Melmed, MD
gil.melmed@cshs.org

Center for Women's GI Medicine/Brown University
146 West River St, 2nd floor
Providence, RI 02904
Silvia Degli Esposti, MD
sdegliesposti@lifespan.org

Children's Hospital Boston
300 Longwood Avenue
Boston, MA 02115
Athos Bousvaros, MD
athos.bousvaros@childrens.harvard.edu

Cleveland Clinic
9500 Euclid Ave./A30
Cleveland, OH 44195
Bret Lashner, MD
Lashneb@ccf.org

Dartmouth-Hitchcock Medical Center
1 Medical Center Drive
Lebanon, NH 03756
Corey Siegel, MD
corey.a.siegel@hitchcock.org

Essentia Health
400 E 3rd St
Duluth, MN 55805
Robert Erickson, MD
robert.erickson@essentiahealth.org

Gastroenterology Associates
44 West River Street
Providence, RI 02904
Samir Shah, MD
samir@brown.edu

Gastroenterology Associates of Central Georgia, LLC
610 Third Street, Ste. 204
Macon, GA 31201
Shahriar Sedghi, MD
gisedghi@aol.com

Lenox Hill Hospital
100 East 77th St. 6th Floor, Black Hall
New York, NY 10075
Burton I. Korelitz, MD
bkorelitzmd@yahoo.com

CLINICAL RESEARCH ALLIANCE newsletter

Massachusetts General Hospital
Gastroenterology Assoc/Digestive Health Center
165 Cambridge Street, 9th Floor
Boston, MA 02114
Deanna Nguyen, MD
dnguyen3@partners.org

Mayo Clinic Rochester
200 1st St SW, 200 1st St SW
Rochester, MN 55905
Edward Loftus, MD
loftus.edward@mayo.edu

Mayo Clinic Florida
4500 San Pablo Road
Jacksonville, FL 32224
John Cangemi, MD
cangemi.john@mayo.edu

Mayo Clinic in Arizona
13400 E. Shea Blvd
Scottsdale, AZ 85253
Jonathan A. Leighton, MD
leighton.jonathan@mayo.edu

Minnesota Gastroenterology
15700 37th Avenue North Suite 300
Plymouth, MN 55446
Robert McCabe, MD
RMcCabe@mngastro.com

Mt. Sinai School of Medicine
Mount Sinai School of Medicine
1468 Madison Ave
New York, NY 10029
Bruce Sands, MD
Bruce.sands@mssm.edu

Penn State College of Medicine
Penn State Milton S. Hershey Medical Center
600 Centerview Drive, PO Box 855, Mail Code A115
Hershey, PA 17033
Andrew Tinsley, MD
atinsley@hmc.psu.edu

Rhode Island Hospital (Brown Med)
University Gastroenterology
33 Staniford Street
Providence, RI 02905
Sheldon Lidofsky, MD
sheldon_lidofsky@brown.edu

University Hospitals Case Medical Center
11100 Euclid Ave.
Division of Gastroenterology and Liver Disease
Cleveland, OH 44106
Jeffry A. Katz, MD
jeffry.katz@uhhospitals.org

University of California, San Francisco
2330 Post Street, #610
San Francisco, CA 94115
Uma Mahadevan, MD
uma.mahadevan@ucsf.edu

University of Chicago
5841 S. Maryland Ave, MC 4076
Chicago, IL 606037
Stephen Hanauer, MD
shanauer@uchicago.edu

University of Cincinnati College of Medicine
231 Albert Sabin Way, ML 0595
Cincinnati, OH 45267
Richard P. Rood, MD
richard.rood@uc.edu

University of Colorado Anschutz Medical Campus
Division of Gastroenterology & Hepatology
12700 E. 19th Ave. MS B-146, RC2 Bldg., #10112
Aurora, CO 80045
Mark Gerich, MD
mark.gerich@ucdenver.edu

University of Florida
1600 SW Archer Road/Box 100214
Gainesville, FL 32610-0214
Sarah Glover, MD
Sarah.Glover@medicine.ufl.edu

CLINICAL RESEARCH ALLIANCE newsletter

University of Iowa
200 Hawkins
Iowa City, IA 52442
David Elliott, MD, PhD
david-elliott@uiowa.edu

University of Kentucky Medical Center
800 Rose Street, Room MN 649
Lexington, KY 40536-0298
Willem J. S. de Villiers, MD
willem.devilliers@uky.edu

University of Maryland
100 North Greene Street
Baltimore, MD 21201
Raymond Cross, MD, MS
rcross@medicine.umaryland.edu

University of Michigan
SPC 5682
1150 West Medical Center Drive
Ann Arbor, MI 48109
Peter Higgins, MD
phiggins@umich.edu

University of Minnesota
2450 Riverside Ave,
Campus Delivery Code 8952C
Minneapolis, MN 55454
Boris Sudel, MD
bsudel@umn.edu

University of North Carolina
Division of Gastroenterology and Hepatology
CB# 7032, Room 7200 MBRB
Chapel Hill, NC 27599-7032
Kim Isaacs, MD
klisaacs@med.unc.edu

University of PA School of Medicine
9th Floor Penn Tower
One Convention Avenue
Philadelphia, PA 19104
Gary Lichtenstein, MD
grl@uphs.upenn.edu

University of Pittsburgh Medical Center
200 Lothrop Street
C-Wing, Mezzanine
Pittsburgh, PA 15213
Jason Swoger, MD
swogerjm@upmc.edu

University of Utah
Division of Gastroenterology
30 N 1900 E 4R118 SOM
Salt Lake City, UT 84132
John Valentine, MD
John.Valentine@medicine.ufl.edu

University of Vermont
67 Maeck Farm RD
Shelburne, VT 05482
James Vecchio, MD
james.vecchio@vtmednet.org

University of Wisconsin
School of Medicine and Public Health
1685 Highland Avenue, Rm
4224 Madison, WI 53705
Sumona Saha, MD
ssaha@medicine.wisc.edu

Vanderbilt University
1211 21st Ave S, Suite 220
Nashville, TN 37232
David Schwartz, MD
david.a.schwartz@vanderbilt.edu

VCUHS Center for IBD
Box 980341
Richmond, VA 23298-0341
Stephen J. Bickston MD, AGAF
sbickston@mcvh-vcu.edu

Wake Forest University School of Medicine
Medical Center Boulevard
Winston-Salem, NC 27106
Richard Bloomfeld, MD
rbloomfe@wfubmc.edu

Wake Research Associates
3100 Duraleigh Road, Suite 304
Raleigh, NC 27612
Charles F. Barish, MD
cfbgastro@aol.com