# CLINICAL RESEARCH ALLIANCE newsletter

CROHN'S & COLITIS FOUNDATION OF AMERICA

## Clinical Research Alliance Meeting

Friday, December 13, 2013
6:30 am - 8:00 am
Westin Hotel, Conference Room 214

**6:30** Breakfast

**6.35** Status of the CRA (H. Herfarth and P. Higgins)

### Update of CRA Studies

**6:45** MERIT-UC (H. Herfarth)

**6:50** PUCCINI (B. Sands and/or B. Cohen)

**6:55** PIANO (U. Mahadevan)

**7:00** MARQUEE (M. Osterman)

### Presentation of the new CRA study

**7:05** Presentation of the new CRA pilot 2014: SPARE (J-F. Colombel)

### Upcoming CRA Studies

**7:15** Adult IBD Quality Improvement Program (G. Melmed and C. Siegel)

### CRA Interest group

**7:25** Biomarker Profiling (R. Stidham and P. Higgins)

**7:35** Closing remarks, discussion

## CRA Interest Group Project
## Serum Biomarkers of Intestinal Fibrosis

PIs: Peter Higgins and Ryan Stidham
University of Michigan

Preliminary single-center proteomic data suggests that as patients with Crohn's disease accumulate intestinal damage, they also express protein biomarkers in their serum. We have found that a group of 5 biomarkers are present in low levels in patients without strictures, increased in patients with fibrotic strictures, and are greatly reduced in these patients after surgical resection. We would like to prospectively test whether this panel of biomarkers can (1) differentiate between patients who have largely inflammatory (B1) and fibrotic (B2/B3) disease; and whether these biomarkers are reproducibly reduced after resection of all damaged segments at the first intestinal resection surgery in Crohn's disease.

We are seeking 10 sites to help us recruit two groups of patients with ages between 12 and 75. One group will have documented active CD with inflammation, and cross-sectional imaging within 30 days with no evidence of obstruction. A single serum sample will be obtained from this group. The second group will have evidence of obstruction on cross-sectional imaging, previous failure of immunomodulator or anti-TNF, and a clinically-indicated surgery in the next 30 days. From this group we will need serum samples within 7-14 days prior to surgery, at 4-8 weeks after surgery, and at 16-24 weeks after surgery. Serum samples will be aliquoted, frozen, and shipped in batches to a central lab for analysis. Case report form data will be entered into a central REDCap database. We are currently seeking funding from the Broad Foundation, though this will be largely for the sample analysis. We are looking for CCFA CRA sites with steady IBD and surgical volumes, an IBD study coordinator, the ability to process, aliquot, and store serum in a -80C freezer, and experience with REDCap is a plus.

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newsletter

# MARQUEE study
# Does Mucosal Healing Matter for Clinically Quiescent Ulcerative Colitis?
# PI: Mark Osterman

## BACKGROUND

There is increasing evidence that patients with ulcerative colitis (UC) have better long-term outcomes, including lower rates of disease flares and also lower rates of hospitalization and surgery, if their gut mucosa is healed. However, no study so far has examined whether treating with medication to the point of mucosal healing irrespective of clinical symptoms is an effective or warranted strategy. The purpose of the proposed study is to determine the proportion of UC patients in clinical remission with active mucosal disease on endoscopy and on histology during routine surveillance colonoscopy. We plan to determine whether the endoscopic activity correlates with biopsy findings. We will then use this information to calculate the risk of clinical disease flare in UC patients depending on their level of endoscopic and histological disease activity. The overall goal is to use all of the above information to plan a large randomized trial in which patients with clinically inactive UC will either remain on 5-ASA medications or step-up to immunosuppressives to determine whether treating with medication to the point of mucosal healing leads to improved clinical outcomes in the long run. We strongly suspect that achieving mucosal healing will lead to better health and quality of life in our UC patients.

## AIMS

### Primary Aims

1. To determine the prevalence of active endoscopic mucosal disease, defined by the Mayo endoscopic subscore, UCEIS, and UCCIS, in patients with clinically quiescent UC undergoing routine surveillance colonoscopy, both prior to and after stratification by baseline UC medication class (5-ASA, thiopurine, anti-TNF)
2. To determine the prevalence of active histological disease (both acute and chronic inflammation), defined by the Riley Index and basal plasmacytosis, in patients with clinically quiescent UC undergoing routine surveillance colonoscopy, both prior to and after stratification by baseline UC medication class (5-ASA, thiopurine, anti-TNF)
3. To correlate the endoscopic findings with histological findings of acute and chronic inflammation

### Secondary Aims

1. To preliminarily determine the risk of clinical relapse by Mayo endoscopic subscore, UCEIS, and UCCIS, in patients with clinically quiescent UC undergoing routine surveillance colonoscopy, both prior to and after stratification by baseline UC medication class
2. To preliminarily determine the risk of clinical relapse by Riley Index and basal plasmacytosis in patients with clinically quiescent UC undergoing routine surveillance colonoscopy, both prior to and after stratification by baseline UC medication class

## STATUS UPDATE

Five sites are involved in the pilot study: University of Pennsylvania (primary), University of North Carolina, University of Michigan, University of Maryland, and Beth Israel Deaconness Medical Center. The protocol has been IRB-approved at all sites. Contracts are nearly finalized at all sites. The database is nearly finalized and testing of the database is about to commence. Start of enrollment is projected to be January 2014.

## RELATED PUBLICATIONS:

Osterman MT. Mucosal healing in inflammatory bowel disease: a review. Journal of Clinical Gastroenterology 2013;47:212-21.

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newsletter

# MERIT-UC MEthotrexate Response In Treatment of UC

PI – Hans Herfarth

## 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 1. 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 2012;30 Suppl 3:112-8.

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.

## 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 32 active sites (if you want to see who is participating check the CRA website). We are still looking for new sites. If you are or know a site that might be interested, please contact Hans Herfarth, PI of MERIT-UC: hherf@med.unc.edu.

## RECRUITMENT

So far we have screened 125 patients for the study and included 79 into the open label induction period. An interim analysis of the open label induction period is planned for mid-January 2014. Currently more thatn 40% of all patients are either in remission or are responding after 16 weeks open label therapy with MTX.

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

PI – Bruce Sands and Ben Cohen

## Rationale

Surgery is common in both Crohn's disease (CD) and ulcerative colitis (UC). There is controversy within the literature as to what the risk factors are for post-operative complications in IBD patients. One of the central questions for which the current literature is heterogeneous is whether use of anti-TNF agents peri-operatively poses a risk for infectious and non-infectious complications. The treatment paradigm for both CD and UC has shifted towards early control of disease with immunosuppressive agents, particularly anti-TNF agents. If anti-TNF agents are found to pose a risk for post-operative complications the management of IBD patients in the peri-operative period would need to be changed.

## Hypothesis

The primary hypothesis is that peri-operative anti-TNF exposure is an independent risk factor for 30 day incidence of post-operative infection in intra-abdominal surgery for CD and UC

## Aims

Aim 1: Determine whether exposure to anti-TNF agents is an independent risk factor for post-operative infection in intra-abdominal surgery for CD and UC

a. Explore use of peri-operative anti-TNF drug levels as a measure of risk for post-operative infection

Aim 2: Determine whether exposure to anti-TNF agents is an independent risk factor for important non-infectious post-operative outcomes in intra-abdominal surgery for CD and UC such as ileus/small bowel obstruction, thromboembolic event, reoperation, and mortality

a. Explore use of peri-operative anti-TNF drug levels as a measure of risk for non-infectious post-operative outcomes

Aim 3: To determine other risk factors associated with post-operative infection in IBD patients undergoing intra-abdominal surgery and explore analytic morphomic measurements as novel predictors of post-operative outcomes.

## Status Update

- The pilot study was completed at Cleveland Clinic Foundation, Massachussetts General Hospital, the Mount Sinai Hospital, University of Michigan Hospital, and University of North Carolina Hospitals.
- Throughout the pilot, study procedures and electronic case report forms were modified.
- Based on the successful pilot study, a CCFA Senior Research Award was awarded to fund the study from July 2013 to July 2016.
- In addition to the pilot sites, seventeen additional centers have committed to participate in the expanded study. These centers include: Boston University Medical Center, Brigham and Women's Hospital, Carle Foundation Hospital, Cedars-Sinai Hospital, Dartmouth-Hitchcock Medical Center, Lenox Hill Hospital, Mayo Clinic Arizona, Mayo Clinic Rochester, Penn State Hershey, University of Chicago, University of California San Francisco, University Hospitals Case Medical Center, University of Colorado, University of Florida, University of Maryland, University of Pennsylvania, University of Pittsburgh, and Wake Forest University.
- The agreement with Prometheus to provide anti-TNF drug level analysis has been finalized.
- Completion of sub-site contracts and submission for sub-site IRB approvals are underway.
- The first patient should be enrolled by January 2014. Over 1000 patients will be enrolled in the final study.

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## PIANO: Pregnancy in Inflammatory Bowel Disease And Neonatal Outcomes

PI – Uma Mahadevan

### PIANO numbers as of 10/30/2013

- Total Patients Enrolled: 1285
- Enrolled in PIANO Extension: 456
- Blood Draws: Check biologic level at birth, month 4,9,12 if levels detected at prior
- 3 received, 7 pending delivery
- 3 more patients interested biologic levels, waiting for consent and waiting on 3 referrals from Vanderbilt
- Vaccine response: All infants after 7 months of age (up to any age) who were vaccinated
- Haemophilus influenza
- Tetanus toxoid
- T and B cell development at 1 year of age
- 30 exposed and 30 unexposed 1-year old infants of IBD mothers studied
- Exposed will be 25 INF/ADA plus AZA/6MP; 5 CZP + AZA/6MP
- Unexposed will be 10 CZP without AZA/6MP; 10 AZA/6mp only; 10 no biologic/IMM
- Additional INF/ADA monotherapy exposed (10)

### Plan for DDW abstracts

- Developmental milestones
- Steroids

### Plan for Manuscripts 2013-14

- Piano pregnancy and newborn outcomes to 1 year
- Asacol safety
- Healthcare maintenance

DECEMBER 2013

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