CLINICAL RESEARCH ALLIANCE newsletter

CROHN'S & COLITIS FOUNDATION OF AMERICA

Clinical Research Alliance Meeting

Monday, May 5, 2014
11.30AM-1.45 PM
Hilton Hotel
720 South Michigan Avenue
Boulevard Room A

11:30 Room open

12:15 Status of the CRA
(H. Herfarth, P. Higgins)

Update of CRA Studies

12:25 MERIT-UC (H. Herfarth)

12:40 PUCCINI (B. Cohen, B. Sands)

12:55 PIANO (U. Mahadevan)

1:10 MARQUEE (M. Osterman)

Presentation of the new CRA study

1:15 High Dose Vitamin D Therapy for Crohn's Disease
(S. Govani, P. Higgins)

CRA Topic

1:25 Universal Contract
(T. Kamphaus, H. Herfarth, P. Higgins, J. Lewis)

1:45 Adjourn

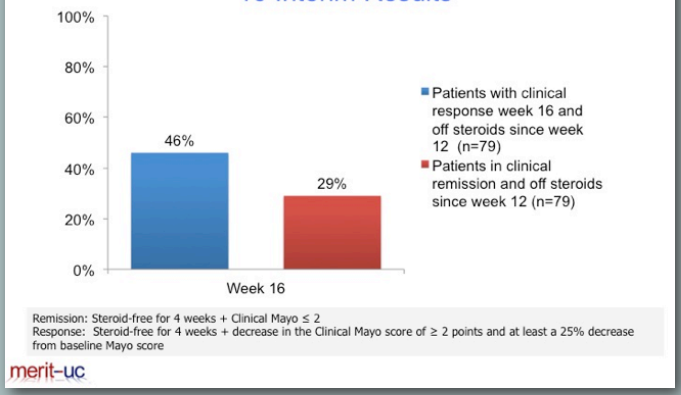
First Exploratory Analysis of MERIT-UC (MEthotrexate Response In Treatment of UC)
PI: Hans Herfarth, M.D., Ph.D.

So far, we have screened 139 patients for MERIT-UC and included 93 into the study. An interim analysis of the open label induction period was performed in January 2014.

The main outcomes for 76 patients completing the open label induction period of 16 weeks are shown in Figure 1. We observed a 46% clinical response rate at week 16. This is remarkable since this endpoint reflects MTX monotherapy 4 weeks after all steroids are stopped at week 12. The steroid free clinical remission rate in MERIT-UC is currently 29%. These are very encouraging numbers, especially if you put this into context with another UC study with a week 16 endpoint - the recently published SUCCESS trial (Figure 2; Panaccione R et al. Combination Therapy With Infliximab and Azathioprine Is Superior to Monotherapy With Either Agent in Ulcerative Colitis. Gastroenterology 2014;146:392-400). The definitions of the endpoints in both studies slightly differ (see Figure 1 and Figure 2). MERIT-UC also included anti-TNF and azathioprine failures, whereas SUCCESS included only anti-TNF naïve patients and patients who were off azathioprine for 3 months or never exposed to azathioprine.

Overall, the data of the open label induction period suggest that MTX has comparable efficacy to azathioprine or anti-TNF therapy to achieve a steroid free remission.

Figure 1: Methotrexate in UC– MERIT-UC Trial: Week 16 Interim Results



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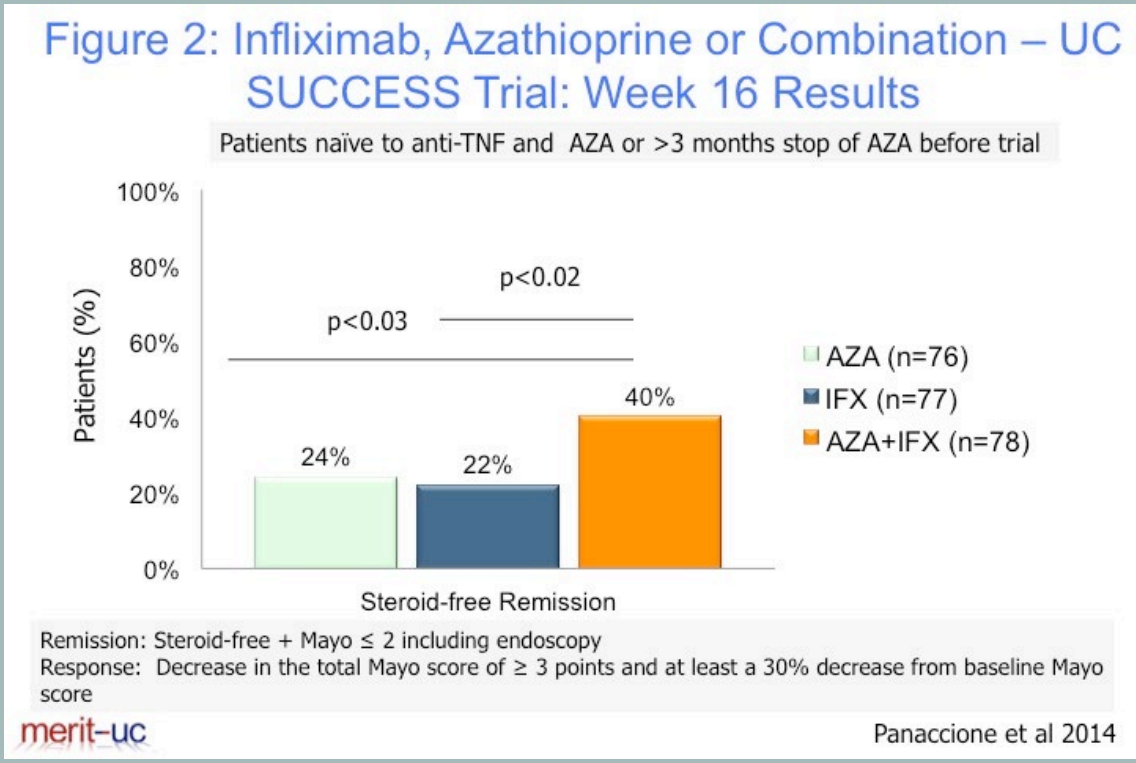
First Interim Analysis of MERIT-UC (MEthotrexate Response In Treatment of UC)

(continued)



The Steering committee of MERIT-UC strongly feels that MTX is a good option for patients with active UC, but we definitely have to complete the trial to define this therapeutic option better in regard to maintenance of remission. Due to the concurrent sampling of DNA and sera we may also be able to predict response and remission with pharmacogenetic and pharmacokinetic analyses in the future. We encourage all sites to continue to actively recruit in the trial, which is the so far largest clinical trial study of the CRA. The currently projected target for the last patient entering the study is May 31 2015.

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.

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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 finalized and has been tested. Start of enrollment is projected to be April 2014.

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PIANO: Pregnancy in Inflammatory Bowel Disease And Neonatal Outcomes

PI – Uma Mahadevan

Enrollment

- 1315 Enrolled as of 3/4/2014
- 482 enrolled in the longterm extension
- Current enrollment is limited to mothers on anti-TNF agents (goal 150)

Check anti-TNF Levels

- New consent form will ask for permission for a release of contact information to UCSF so we can mail them the kits
- Anti-TNF levels will be checked at birth in mother, cord and infant. If levels detectable, will check infant at 3 months; if detectable at 6 months.
- If you have a patient enrolled who is on anti-TNF therapy will be eligible for this. We would really LOVE to capture these patients.
- 12 patients have delivered, 23 more waiting to deliver

Optional

- If a patient is on anti-TNF we would like to check breast milk samples in a small number of patients. Ideally the tubes will be mailed out with the kits for delivery. These kits will be mailed to the patient in the third trimester with a copy of her consent form and a letter to the OB with instructions
- 15 breastmilk results received
- Response to vaccines will also be measured in all infants greater than 7 months of age. This is part of standard of care to see if they responded to their vaccines given immunosuppression use. We can enroll any existing PIANO patients in this regardless of medication exposure. We are targeting 300-400 patients.

Not yet started

- T and B cell development. This is a substudy, separately funded, where we are measuring T and B cell development in children exposed to anti-TNF in utero. We are looking for specific populations.
- 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

Three abstracts accepted as oral presentations at DDW

- Achievement of Developmental Milestones Among Offspring of Women with Inflammatory Bowel Disease: The PIANO Registry
- Exposure to anti-TNFα therapy in the Third Trimester of Pregnancy is Not Associated with Increased Adverse Outcomes: Results from the PIANO Registry
- Pregnancy outcomes amongst mothers with inflammatory bowel disease exposed to systemic corticosteroids: Results of the PIANO Registry

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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

- Funding for the CCFA Senior Research Award began in July 2013.
- Contract agreement was reached with Prometheus Labs to provide anti-TNF level analysis free for the study.
- Sub-site agreements are currently being finalized with the individual sites. Participating centers include: Boston University Medical Center, Brigham and Women's Hospital, Carle Foundation Hospital, Cedars-Sinai Hospital, Cleveland Clinic Foundation, Dartmouth-Hitchcock Medical Center, Lenox Hill Hospital, Massachusetts General Hospital, Mayo Clinic Arizona, Mayo Clinic Rochester, the Mount Sinai Hospital, 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 Michigan Hospital, University of North Carolina Hospitals, University of Pennsylvania, University of Pittsburgh, and Wake Forest University.
- Sites will be paid $250 per patient enrolled with an enrollment cap of 150 patients for any one center.
- Site initiation meeting will be planned for DDW in May at which time investigators can be oriented for the beginning of enrollment.
- Sites will be expected to participate in 2 conference calls per month during the patient enrollment phase.

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