CLINICAL RESEARCH ALLIANCE newsletter

CROHN'S & COLITIS FOUNDATION OF AMERICA

Clinical Research Alliance Meeting

Friday, December 5, 2014
6:30 - 8:00 AM
Hilton Orlando
6001 Destination Parkway, Orlando
Room: Lake Virginia

6:30 Breakfast
6:35 Status of the CRA
(H. Herfarth, P. Higgins)

Update of CRA Studies

6:45 MERIT-UC (H. Herfarth)
6:50 PUCCINI (B. Cohen, B. Sands)
6:55 MARQUEE (M. Osterman)
7:00 RODIN - CD (S. Govani)
7:05 Presentation of the two 2014/2015 CRA pilots (J. Lewis, M. Long)

CRA Collaboration

7:20 GEM (K. Croitoru)

Future Developments CRA

7:25 CCFA IBD Partners Program
(J. Lewis)

CRA Internal Topic

7:35 CRA Authorship Rules
(P. Higgins, H. Harfarth)
7:40 - 7:50 Discussion of Authorship Rules

RODIN-CD: A Randomized Controlled Trial of High-Dose Vitamin D in Crohn's Disease

PI: Shail Govani

Rationale

Patients with Crohn's disease (CD) are often vitamin D-deficient. Epidemiological and retrospective evidence exists to suggest that vitamin D levels play a role in the pathogenesis and disease activity of Crohn's disease (CD). While one small randomized controlled trial showed a trend towards reduction in relapse among patients given low doses of cholecalciferol, it remains unclear whether correction of vitamin D deficiency improves CD outcomes.

Hypothesis

We hypothesize that high dose vitamin D supplementation (10,000 IU for 60 days) among CD patients with vitamin D deficiency (serum 25-OH <20 ng/ml) does not cause hypercalcemia and improves clinical outcomes compared to supplementation with 400 IU daily for 60 days.

Aims

Aim 1: Compare clinical outcomes (CD-related surgery, CD-related hospitalizations, CD-related Emergency Department visits, and steroid prescriptions) between patients given high dose vitamin D3 versus low dose vitamin D3.

Aim 2: Compare adverse event rates (hypercalcemia and nephrolithiasis) between patients with patients given high dose vitamin D3 versus low dose vitamin D3.

Update

Since receiving funding, an FDA IND has been granted and the IRB has approved the study at the University of Michigan. Partnering sites at the University of North Carolina, Indiana University and University of Iowa are in the process of preparing IRB applications. Subcontracts with the partnering sites are being prepared.

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MERIT-UC (MEthotrexate Response In Treatment of UC)

PI: Hans Herfarth

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.

So far we have screened 180 patients for the study and included 121 into the study. An interim analysis of the open label induction period was performed in January 2014 revealing a steroid-free 46% clinical response rate and 29% steroid free remission rate at week 16. Both of these endpoints reflect MTX monotherapy for 4 weeks since steroids are stopped at week 12. Now over 100 patients have completed the Induction Period and the response and remission rate remain stable around 50% and 30% respectively.

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. **We need to include only approx. 50 more patients in the trial to complete enrollment.** The currently projected target for the last patient entering the study is May 31 2015.

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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 study started enrolling April 2014, and as of 10/23/14, 53 of the planned 100 patients have been enrolled, with 12 patients having completed the 3-month follow-up visit.

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PIANO: Pregnancy in Inflammatory Bowel Disease And Neonatal Outcomes

PI - Uma Mahadevan

PIANO numbers as of 10/17/2014

- Total Patients Enrolled: 1378
- Enrolled in PIANO Extension: 534
- Blood Draws: Check biologic level at birth, month 4,9,12 if levels detected at prior
  - 43 received (including infants) 19 pending delivery
  - Begin enrolling patients on newer drugs including ustekinumab (stelara), vedolizumab (entyvio) and golimumab (simponi) to monitor safety in these agents
- Obtain breast milk samples in at least 10 patients per biologic (protocol for 1,12,24,48,72,96,120,168 hours)
  - 31 samples (14 infliximab, 8 adalimumab, 8 certolizumab, 1 natalizumab.)
- Vaccine response: Actively recruiting 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:

1. Breastmilk
2. Association of maternal weight gain and preterm birth

Plan for Manuscripts 2014-5:

1. Piano pregnancy and newborn outcomes to 1 year
2. Asacol safety
3. Healthcare maintenance
4. Breastmilk

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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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