Corticosteroids as Co-Induction Agents With Vedolizumab in Crohn's Disease: a Double-blind Placebo Controlled Randomized Trial
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CONSULTANTS: None

ESTIMATED DURATION OF STUDY: 2 Years

NUMBER AND TYPE OF PATIENTS: 123 ambulatory patients with acute, moderate to severe Crohn's disease starting vedolizumab therapy

SUBJECTS OF STUDY:

Number	123 patients
Sex	Male & Female
Age Range	above 18 years

PROJECT USES IONIZING RADIATION: No

PROJECT USES "DURABLE POWER OF ATTORNEY": No

OFF-SITE PROJECT: Yes

MULTI-INSTITUTIONAL PROJECT: Yes

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1) Introduction

Crohn's disease (CD) is a chronic inflammatory disorder of the alimentary tract. Treatment with TNFα antagonists has substantially improved the care of patients with CD that are refractory to other conventional treatments such as azathioprine, 6-mercaptopurine, methotrexate, corticosteroids, and mesalamine. However, a majority of patients will still not be in remission at 1 year after initiation of TNF antagonists (1, 2). Further, TNF antagonists have a higher risk of several serious infections including tuberculosis and may increase the risk of certain malignancies.

The GEMINI 2 study was a randomized controlled trial that established the efficacy and safety of vedolizumab induction and maintenance therapies. GEMINI-3 focused on use of vedolizumab in anti-TNFα failures. Both of these studies showed promise of vedolizumab for induction and maintenance of patients with active Crohn's disease (3, 4). However, the rate of clinical remission at week 6 was only 15.2% in those given vedolizumab and 12% in those on placebo (p=0.433)(4). In both studies, benefits became more apparent by week 10.

1.1) Hypothesis:

Use of co-induction with corticosteroid therapies may accelerate the remission rate when used with vedolizumab. Further, this may lead to higher rates of response and remission at week 10 than would be seen with vedolizumab monotherapy.

2) Background and Rationale

Vedolizumab has been shown to be effective as an inductive agent in Crohn's disease. The rate of clinical remission at week 6 after vedolizumab 300 mg IV at weeks 0 and 2 is 14.5% vs. 6.8% for placebo in GEMINI 2, a population comprising 50% of patients with TNFα antagonist failure (3). In GEMINI 3, the rate of clinical remission at week 6 in the TNFα antagonist failure population was 15.2% compared to 12.1% assigned to placebo, while the TNFα antagonist naive subgroup achieved 31.4% clinical remission at week 6 with vedolizumab and 12.0% with placebo (4). By contrast, at week 10 (after a 3rd induction dose at week 6), 26.6% of TNFα antagonist failure patients and 35.3% of TNFα antagonist naive patients assigned to vedolizumab achieved clinical remission, compared to 12.1% and 16.0% assigned to placebo respectively. These findings suggest that a third inductive dose of vedolizumab and/or additional passage of

time are helpful in increasing the inductive efficacy of vedolizumab in Crohn's disease patients, and particularly so among TNFα antagonist experienced patients. Vedolizumab has been shown as well to be effective in maintaining remission among patients with Crohn's disease who achieve clinical response at week 6. However, these relatively long induction periods and relatively low rates of clinical remission suggest the need to explore other inductive therapies as a co-inductive strategy in Crohn's disease. If successful, identifying such a co-inductive therapy might ultimately increase the long term success of vedolizumab therapy by enhancing the proportion of patients achieving clinical remission and accelerating time to remission.

Corticosteroids have long been used with success as inductive agents in Crohn's disease. No agents yet studied, including anti-TNFα antagonists, demonstrate a faster time to response. One study of prednisone co-induction with infliximab noted higher than anticipated rates of remission than had been observed historically with infliximab alone (5). Systematic review and meta-analysis in Crohn's disease demonstrate rates of clinical remission with inductive corticosteroids between 43 and 83% (6). This experience suggests that a strategy of corticosteroid co-induction with vedolizumab might increase the proportion and rapidity of clinical remission in Crohn's disease. On the other hand, corticosteroids are associated with well-known side effects even with short term use. Furthermore, there is some evidence that corticosteroids may inhibit mucosal healing, raising the possibility that with corticosteroid co-induction, short term clinical remission might be achieved at the expense of mucosal healing and longer term disease outcomes (7, 8). Finally, much has yet to be learned about the mechanism of action of vedolizumab in Crohn's disease in order to account for the apparently longer time to achieve clinical remission than in UC, and the effects on mucosal immunity.

To address these concerns, we propose to study a strategy of prednisone co-induction with vedolizumab in patients with Crohn's disease. To address questions regarding the effect of co-induction on mucosal healing, we propose to include colonoscopic assessment of mucosal healing in this study. Finally, the opportunity to obtain colonic biopsies in this study will allow us to elucidate further the mechanism of action of vedolizumab in Crohn's disease.

3) Specific Aims

1. To determine whether a prednisone taper, when added as co-inductive therapy, increases the proportion of patients with Crohn's disease who achieve clinical remission at week 6 after induction therapy with vedolizumab 300 mg IV at weeks 0 and 2, as compared to placebo co-induction.

2. To determine if the rate of endoscopic response, defined as decrease from baseline SES-CD by 50%, at week 10 is higher with prednisone vs. placebo co-induction in conjunction with vedolizumb given at weeks 0, 2 and 6.

3. To describe the mucosal and peripheral immunophenotypic changes with vedolizumab therapy in Crohn's disease both with and without prednisone co-induction.

4) Overall Study Design

This is a prospective, blinded, interventional, placebo-controlled study designed to define the impact of co-intervention with prednisone when offering induction therapy with vedolizumab in Crohn's disease. The interventional component of the study will assess remission rates at weeks 6 and 10 of patients who receive a combination of prednisone and vedolizumab compared to those who receive vedolizumab monotherapy.

4.1) Study timeframe

123 patients with moderate to severe Crohn's disease will be enrolled, with study activities expected to last 18 months.

5) Study Methods

5.1) Recruitment

Patients will be recruited through the outpatient clinics and personal clinics of the study investigators. Recruitment will also be achieved through the gastroenterology practices affiliated with each recruiting institution. The faculty or gastroenterology fellows at the participating institutions will identify eligible patients from the ambulatory or inpatient setting. Patients identified in the IBD ambulatory clinics with moderate to severe Crohn's disease and needing treatment with vedolizumab will be screened for eligibility during the ambulatory visit. The gastroenterology fellow involved in the study at

each site will send weekly email reminders to the gastroenterologists to encourage recruitment. Additionally, recruitment for the study will be achieved through the circulation of pamphlets and a dedicated website. Consecutive ambulatory patients with moderate to severe Crohn's disease meeting inclusion/exclusion criteria will be enrolled after written informed consent is obtained.

5.2) Informed Consent

We will follow Mount Sinai's "SOP HRP-090 Informed Consent Process for Research" and "SOP HRP-091 Written Documentation of Consent." Potential participants will be presented with the opportunity to participate in the study. Those interested in participating will be introduced to the study procedures and will be given the opportunity to have their questions answered. Potential participants will also be counseled about who may have access to their medical and other personal information so as to remain in compliance with HIPAA standards. Patients agreeing to participate will provide written consent during the screening ambulatory visit. The consent process will be executed by one of the investigators or one of the trained research staff. No research data or labs will be collected prior to obtaining written informed consent. The signed original consent form will be retained in the research files in the research office, in a locked file cabinet in a locked office. A copy of the signed consent form will be provided to the subject. Non-English speaking patients will be excluded from the study.

5.3) Inclusion Criteria

1. Age at entry 18 to 70
2. CDAI score ≥220 and ≤ 450
3. Concomitant azathioprine, methotrexate, or mercaptopurine permitted if dose has been stable for ≥ 8 weeks. Prior anti-TNFα antibody use permitted but must be discontinued (≥2 weeks from last dose) prior to initiation of vedolizumab. Concomitant oral antibiotics for Crohn's disease therapy are permitted if dose has been stable for ≥ 2 weeks. Concomitant rectal therapies (suppositories or enemas) are permitted if dose has been stable ≥ 2 weeks. Prior use of cyclosporine and natalizumab is permitted if last use is at least 3 months prior to the initiation of vedolizumab.
4. Screening colonoscopy SES-CD score ≥ 7 or ≥ 4 if isolated ileal disease.

5. Able to provide written informed consent.

5.4) Exclusion Criteria

1. Concurrent use of anti-TNFα antibodies.
2. Corticosteroids within prior 3 months (other than budesonide controlled ileal release and budesonide extended release tablets)
3. Stoma at the time of enrollment
4. Absolute contraindication to systemic corticosteroid use such as hypersensitivity to any part of the formulation, systemic fungal infection, or recent administration of live or live attenuated vaccine within prior two weeks.
5. Pregnant women or plans for pregnancy within 3 months of study inclusion
6. Presence of stoma, more than three small-bowel resections, or documented history of short bowel syndrome
7. Intestinal stricture requiring surgery
8. Abdominal abscess
9. Inability or unwillingness to provide informed consent
10. Any other condition, which, in the opinion of the investigators would impede competence or compliance or possibly hinder completion of the study

5.5) Plan for Women and Minorities

All consecutive subjects at a site consenting to the study, including women and minorities, will be enrolled. Subjects will not be excluded because of gender or race.

5.6) Crohn's disease Management

This is an interventional study of co-administration of corticosteroids with vedolizumab. Management of Crohn's disease outside the scope of this will be at the discretion of the treating gastroenterologist based on their clinical judgment. Examples of management at the discretion of the treating physicians include continuing concurrent use of other IBD medications (i.e. 5-ASA drugs or immunomodulators).

5.7) Subject Discontinuation

Subjects may withdraw their consent at any time during the study by informing one of the investigators or the study coordinator of the decision. Subjects who withdraw consent will not undergo any further study procedures.

The sponsor may terminate the study at any time for any reason, including but not limited to unsatisfactory accrual or data collection.

6) Sample Collection and Storage

6.1) Blood Sample Collection

Regardless of whether blood is drawn from an intravenous line or by separate venipuncture, standard sterile methods will be utilized. The following sample types will be collected during the study:

- Serum (SST vials): Immune phenotyping markers, C-reactive protein (CRP), comprehensive metabolic panel, and albumin will also be collected in SST vials at specified time points.
- Whole blood (EDTA Spray-dried vials): Complete blood count with differential and immune phenotyping markers will be collected at specified time points.

Blood samples will be collected using a 21 gauge butterfly needle to avoid backflow as the collection vials contain chemical additives. Blood samples will be drawn in the following order: 1) SST collection vial(s); 2) EDTA spray-dried collection vial(s); 3) EDTA collection vial(s).

6.2) Blood Sample Labeling

Specimens will be labeled with the donor's study number and the date that the specimen was collected.

6.3) Blood Sample Storage

All blood and tissue specimens may be stored for up to two years for analyses. Blood samples will be stored under appropriate conditions in the locked laboratory of Dr. Saurabh Mehandru at the Icahn School of Medicine at Mount Sinai.

6.4) Blood Sample Preparation

The vials will be processed as follows:

- SST collection vials: The vials will be spun in a fixed angle or swing bucket type centrifuge, inverted 5X, allowed to stand for 30 minutes (to allow for clotting), and then centrifuged for 15 minutes at 1100-1300 x g.
- At baseline and specified time points for assessment of disease activity 5.0 mL whole blood (EDTA) will be collected.
- At baseline, blood (5X10 ml EDTA and 1X10ml SST tubes). Briefly, PBMC will be isolated per density gradient. 5X10^6 PBMC will be used per condition (baseline, cultured and stimulated, cultured and unstimulated) for CYTOF analyses (described separately). SST tubes (1X10ml) will be processed as above for serum collection for assessment of serum cytokines and soluble markers of inflammation.

6.5) Measurement of Disease Activity Markers

Serum (1.0 mL) and whole blood (5.0 mL) will be collected at specified time intervals for CRP, CBC with differential or metabolic panel as specified in section 7.1. Additional blood (62.5 mL) will be collected at the beginning of treatment and during specified time points detailed in the protocol schedule of events (appendix 1) to evaluate the phenotype and function of innate and adaptive immune cells.

Immunophenotypic analyses

Immunophenotyping of the peripheral blood and GI tissue will be performed on 60 patients (30 patients on Vedolizumab induction and 30 patients on Vedolizumab plus prednisone induction) due to feasibility issues. Please see accompanying document "Phenotyping peripheral blood and gastrointestinal immune subsets using mass cytometry (CyTOF)" for details. The following markers will be assessed:

a) **Phenotypic markers:** CD19 (B cells), CD4 and CD8 subsets of T cells, CD16 (monocytes, NK cells), CD56 (NK cells) CD66 (neutrophils, basophils), CD14 (monocytes, neutrophils, dendritic cells), BDCA1 (CD1a dendritic cells), CD123 (plasmacytoid dendritic cells, basophils), BDCA3 (CD141 cross presenting dendritic cells)

b) **Immunological memory markers:** CD45 (hematopoietic cells), CD45 RA (naïve vs. memory), CD27 and CCR7 (central memory vs. effector memory vs. transitional memory)
c) **Cellular activation markers:** HLA-DR, CD38
d) **Cytokine production:** TNF-a, IFN-g, IL-6, IL-17A, IL-10

Measurement of cytokines will be performed in PMA/ionomycin stimulated cells.

6.6) Tissue Sample Collection

Colon biopsy specimens will be collected using jumbo biopsy forceps. A total of 16 colonic biopsies will be collected: eight from the inflamed and eight from uninflamed areas. From each set of 8 eight biopsies, 1 each will be sent for histopathology and the remainder will be used for analyses of immunophenotypic changes as described below. The biopsies will be collected at baseline (screening visit 2) and at week 10. If at week 10 colonic inflammation is not noted, a total of 16 biopsies will be obtained from the previously inflamed area. For analyses by H&E, the biopsies will be obtained in formalin and processed by the Department of Pathology at each institution. For immunological analyses, all biopsies will be processed in the laboratory of Dr. Saurabh Mehandru at the Icahn school of Medicine at Mount Sinai. Briefly, collagenase type IV will be used to digest the biopsies using gentle agitation at 1000 rpm for one hour. After extensive washing and filtration, mucosal mononuclear cells (MMC) will be obtained as per established protocols (9). Using metal conjugated antibodies, phenotypic and functional markers will be examined on the MMC (see additional details re CYTOF).

6.7) Stool Sample Collection

Stool specimens for calprotectin must be collected in sterile containers. Specimens will be collected at baseline, at week 6 and at week 10. A minimum of 1 gram of stool is required. Samples will be labeled with the donor's study number and stored in a -70 freezer in Dr. Saurabh Mehandru's laboratory at Ichan School of Medicine at Mount Sinai.

7) Study drug / Additonal agent

The study drugs/substances used in this study include Prednisone/placebo. Vedolizumab will be given on a standard of care basis as an additional agent.

7.1 Prednisone / Placebo

The research pharmacy at The Icahn School of Medicne at Mount Sinai will prepare and dispense 5 weeks supply (98 capsules) of the study drug. The subject will receive all the study medication (prednisone/placebo) in one batch.

Prednisone/Placebo is prepared and dispensed according to the dosing schedule:

- Week 0: 40 mg daily
- Week 1: 40 mg daily
- Week 2: 30 mg daily
- Week 3: 20 mg daily
- Week 4: 10 mg daily

7.2 Vedolizumab (Additional Agent):

All subjects enrolled in the study will receive Vedolizumab. Vedolizumab will be administered as standard of care at an infusion center agreed upon by the Gastroenterologist and the subject. Subjects will be administered 300mg IV Vedolizumab over 30 minutes using standard infusion procedures at Week 0, Week 2 and Week 6.

Prednisone/Placebo and Vedolizumab must be started on the same day at Week 0.

8) Study-Related Assessments

Study activities are summarized in appendix 1. Screening visits 1 and 2, and the week 0 assessment will be conducted by one of the investigators or the study coordinator.

8.1) Screening Visit #1

Screening of all patients with moderate to severe Crohn's disease will occur in the ambulatory clinic. If a patient is felt suitable for inclusion, during the screening visit the following activities will occur:

1) Obtain informed consent
2) Review inclusion/exclusion criteria

3) Confirm Crohn's disease diagnosis

4) Demographic information collected:

   a. Age/Date of Birth
   b. Gender
   c. Race
   d. Ethnicity
   e. Smoking History

5) Full disease history:

   f. Year of diagnosis
   g. Duration of disease
   h. Prior Crohn's related surgery
   i. Location of Crohn's disease
   j. Duration of current flare
   k. Number of draining fistulas, if applicable
   l. Presence of active extra-intestinal manifestations

6) Record past and present use of Crohn's disease related medications. The following information will be collected for each medication

   m. Name
   n. Dose
   o. Route
   p. Frequency
   q. Start date
   r. Stop date
   s. Reason for stopping (i.e. loss of response, intolerance, patient preference, etc)

7) Administer and collect disease-related activity indices (See appendix 2)

   a. Current CDAI score (appendix 2)

8) Abstract laboratory data (performed as standard of care) and blood draw
   a. Standard of Care Labs
      i. CBC with diff
      ii. Comprehensive metabolic panel including electrolytes, albumin, renal function, and hepatic function

9) Subjects will be provided a kit for collection of stool for measurement of fecal calprotectin. This specimen will be collected at screening visit number 2.

10) Subjects will be given preparation instructions for baseline screening colonoscopy to be completed at screening visit number 2.

11) Subjects will be asked to sign a medical release that will allow us to request medical records from on-site and off-site medical providers if necessary. Subjects will provide the name(s) and contact information for each physician involved in treating his/her Crohn's disease.

8.2) Screening Visit #2

The second screening visit will occur at time of the baseline colonoscopy. Patients will arrive after taking a preparation for colonoscopy. During this visit the following activities will occur:

1) Collection of fecal calprotectin sample
2) Abstract laboratory data (performed as standard of care) and blood draw for immune phenotyping
    a. Research Labs
        i. Blood
            1. CRP
            2. Immune subsets and cytokine levels
3) Perform baseline colonoscopy to assess disease severity and distribution (performed as standard of care). The SES-CD tool (appendix 3) will be used to quantify and compare inflammatory load. Biopsies may be taken for histopathology as well as for immune phenotyping as mentioned in section 6.6.

4) Video recordings of the colonoscopy will be performed to allow for scoring the amount of inflammation seen during the procedure. The video will only be from the inside of the colon and not contain any images that would personally identify any subject. Additionally, to protect subject's confidentiality, any unique identifierssuch as subject's name will be removed from the recording. Finally, the recording will be stored in an electronic hard drive, under lock and key.

Subject will be given a kit for collection of fecal calprotectin the day prior to the week 6 visit. They will be sent a reminder email two days prior to the week 6 visit.

8.3) Randomization

1. Randomization into the study will be done through the Research Pharmacy at the Icahn School of Medicine at Mount Sinai. Once a patient is deemed eligible for randomization in the study, a Mount Sinai medical record number will be requested and assigned to the patient to facilitate drug preparation and dispensation from the

pharmacy at the Icahn School of medicine at Mount Sinai. Patients will be randomized in a blinded fashion, 1:1 to one of two groups, in a method that stratifies for:

a) Prior anti-TNFα use

b) Concomitant immune modulator use

Group A: Prednisone 40 mg/day starting at week 0 for 2 weeks, tapered by 10 mg weekly to achieve 0 mg by end of week 5

Group B: Identical placebo taper (40 mg/day starting at week 0 for 2 weeks, tapered by 10 mg weekly to achieve 0 mg by end of week 5

Upon randomization, patients will be dispensed all study pills for the arm they are randomized to during this study visit.

8.4) Week 0: Vedolizumab Dose #1

The week 0 visit should occur within one week after the screening colonoscopy confirms eligibility. The week 0 activities will be conducted by study personnel or one of the study investigators.

A) Prior to administration of vedolizumab, the following activities will occur:

1) History and physical examination to assess for signs of active, untreated infection

B) Following the pre-infusion activities, the patient will be administered 300mg IV vedolizumab over 30 minutes using standard infusion procedures at Mount Sinai.

8.5) Week 2: Vedolizumab Dose #2

The week 2 visit should occur two weeks after receipt of initial vedolizumab dose. The week 2 activities will be conducted by study personnel or one of the study investigators.

A) Prior to administration of vedolizumab, the following activities will occur:

1) History and physical examination to assess for signs of active, untreated infection

B) Following the pre-infusion activities, the patient will be administered 300mg IV vedolizumab over 30 minutes using standard infusion procedures at Mount Sinai

8.6) Week 6: Vedolizumab Dose #3

The week 6 visit should occur four weeks after the week 2 visit. The week 6 activities will be conducted by study personnel or one of the study investigators.

A) Prior to administration of vedolizumab, the following activities will occur:

1) History and physical examination to assess for signs of active, untreated infection. Other screening questions will be asked to screen for side effects related to prednisone use.
2) Administer and collect disease-related activity indices
    a. Current CDAI score (appendix 2)
3) Abstract laboratory data (performed as standard of care) and blood draw for immune phenotyping

    a. Standard of Care Labs
        i. CBC with diff

    b. Research Labs

        i. Blood
            1. CRP
            2. Immune subsets and cytokine levels

        ii. Stool
            1. Fecal calprotectin (patient will have brought sample performed the day previously)

B) Following the pre-infusion activities, the patient will be administered 300mg IV vedolizumab over 30 minutes using standard infusion procedures at Mount Sinai

C) Patient will be given a kit for collection of fecal calprotectin the day prior to the week 10 visit. They will be sent a reminder email two days prior to the week 10 visit.

D) Patient will also be given instructions for their colonoscopy to be performed at week 10.

8.7) Final study visit at week 10

The week 10 visit should occur four weeks after the week 6 visit. The week 10 activities will be conducted by study personnel or one of the study investigators.

A) Prior to colonoscopy, the following activities will occur:

1) History and physical examination to assess for signs of active, untreated infection. Other screening questions will be asked to screen for side effects related to prednisone use.
2) Administer and collect disease-related activity indices
    a. Current CDAI score (appendix 2)
3) Abstract laboratory data (performed as standard of care) and blood draw for immune phenotyping

    a. Standard of Care Labs
        i. CBC with diff

    b. Research Labs

        i. Blood
            1. CRP
            2. Immune subsets and cytokine levels

        ii. Stool
            1. Fecal calprotectin (patient will have brought sample performed the day previously)

B) Perform week 10 colonoscopy to assess disease severity and distribution. The SES-CD tool (appendix 3) will be used to quantify and compare inflammatory load with baseline colonoscopy. Biopsies may be taken for histopathology as well as for immune phenotyping as mentioned in section 6.6.

C) Video recordings of the colonoscopy will be performed to allow for scoring the amount of inflammation seen during the procedure. The video will only be from the inside of your colon and not contain any images that would personally identify you. Additionally, to protect your confidentiality, any unique identifiers such as your name will be removed from the recording. Finally, the recording will be stored in an electronic hard drive, under lock and key.

D) Patient will be provided stipend at this visit to reimburse them for all their study visits. This includes $50 for the week 0, 2, and 6 visits. This also includes $200 for the screening visit #2 and week 10 visits. Payments will only be provided for study visits that were completed.

9) Plan for Data Collection and Management

The collection and management of the data from all sites will be through an online computer website and database at the Icahn School of Medicine at Mount Sinai. Hard copies of data collection forms will be completed at each participating institution and submitted to the Icahn School of Medicine to be entered in the electronic database. Data collection forms will not contain patient names, medical record numbers, or any other identifiable information. Data collection forms will contain an assigned study number. Copies of all consent forms and data collection forms will also be kept at the individual sites in locked cabinets for secure back-up.

10) Statistical Considerations and Sample Size

10.1) Sample Size

The primary outcome is clinical remission defined as a CDAI $\leq$ 150 at week 6. Using a conservative estimate of 45% in group A and 19% in group B, 56 patients are needed per group for 80% power at a 2-sided alpha of 0.05. Factoring in an additional 10% to account for possible dropout, the total number of targeted enrollment is 123 patients.

Approximately 7000 patients per year are seen at Mount Sinai Hospital for Crohn's disease or ulcerative colitis, many of whom have active symptoms requiring change in management. With a targeting enrollment of 123 patients, we estimate roughly 10 patients will be enrolled per month, which would allow for completion by 14 months.

10.2) Study Endpoints

Primary Endpoint:

1) Week 6 clinical remission, defined as CDAI $\leq$ 150, in group A vs. group B

Secondary Endpoints:

1) Week 10 clinical remission (CDAI $\leq$ 150) in each group
2) Week 6 clinical response (decrease in CDAI $\geq$ 100 from baseline) in each group
3) Week 10 clinical response (decrease in CDAI $\geq$ 100 from baseline) in each group
4) Comparison of the proportion of patients in each group achieving week 10 SES-CD decrease of $\geq$ 50% from baseline
5) Comparison of absolute change from baseline in SES-CD in each group at week 10
6) Comparison of absolute change from baseline in CDAI in each group at week 6
7) Comparison of absolute change from baseline in CDAI in each group at week 10
8) Adverse events in each group at week 6
9) Adverse events in each group at week 10
10) Comparison of absolute change from baseline CRP in each group at week 6

11) Comparison of absolute change from baseline CRP in each group at week 10
12) Comparison of absolute change from baseline calprotectin in each group at week 6
13) Comparison of absolute change from baseline calprotectin in each group at week 10
14) Descriptive analysis related to mechanism of action using peripheral blood and intestinal mucosal tissue

10.3) Statistical Analysis

Predictors of the endpoints listed above will be explored. Potential predictors to be assessed include:

1) Age
2) Gender
3) Ethnicity
4) Current smoker (yes/no)
5) Past smoker (yes/no)
6) Duration of disease
7) Duration of current flare
8) Extent of disease (ileal only, ileocolonic, upper GI tract, colon only)
9) Concomitant meds
    a. Immunomodulator (yes/no)
    b. 5-ASA (yes/no)
    c. Prior anti-TNFα use (yes/no)
10) Baseline CDAI score
11) Baseline CRP
12) Baseline fecal calprotectin
13) Research disease activity markers

11) Data Monitoring Plan

Study data will be collected at each site and submitted to the coordinating site (ISMMS). The Investigators and research coordinators of this protocol at each site will monitor data and safety regularly at weekly meetings. These meetings are separate from regular clinical rounds and consist of review of all study patients including flow sheets of major safety and efficacy measurements.

From a central stand point, bi-monthly conference calls between participating sites will take place to monitor the study data. The principal Investigator will lead the conference calls and at least one member of each site team will be present for the call. Safety data/Serious adverse events will be submitted to Mount Sinai as they occur. Accumulated data and safety information will be evaluated by the Principal monitor and the additional monitor at Mount Sinai on a weekly, as outlined in the Protocol Template.

There is not a DSMB established for this study. The rationale for not using an outside data and safety monitoring committee is that the drug being used is FDA approved medication that have been associated with few severe side effects. All measurements and tests are well established in clinical medicine. All serious adverse events will be reported to the Mount Sinai IRB within 2 days.

12) Hazards and Discomforts

The risks and discomforts of frequent phlebotomy:

To document changes in levels of biochemical markers of inflammation and to monitor the metabolic effects of vedolizumab, frequent blood sampling will be required. Patients will have a maximum of 5 venipunctures during the period of evaluation, therapy and follow up. Each venipuncture will remove 15 to 50 ml of blood. Blood collection by venipuncture is associated with mild discomfort, and the possibility of localized bruising, phlebitis, or extravasation. The risk of infection or fainting is extremely small.

The risks and discomfort of colonoscopy:

A colonoscopy will be performed before commencement of vedolizumab and after 10 weeks of treatment. Preparation for the procedure will involve taking a standard preparation for colonoscopy at the discretion of the treating gastroenterologist. Commonly used preparation at Mount Sinai Hospital is Polyethylene glycol 3350 – 238 grams mixed with a clear fluid such as water or Gatorade. There is a slight risk of dehydration with taking colonoscopy preparation. The procedure itself lasts between 5 and 20 minutes. During the procedure the patient may feel pressure and slight cramping in the lower abdomen. Colonoscopy is a safe procedure, but does carry small risks of perforation, bleeding, infection, and adverse reaction to conscious sedation if used. The risk of perforation in colonoscopy is approximately 1 in 1400 (10).

Potential Loss of Confidentiality:

Every effort will be made to protect privacy and confidentiality. Patient-related information (i.e. informed consent, medical records) will be kept in a locked filing cabinet in the PI or study coordinator's office or on a password protected computer. No information related to this research testing will be entered into a computer database that identifies the patient by name or any other identifying information. To minimize the risk

of misuse of these data, only personnel authorized by the Principal Investigator will have direct access to the study database.

Similarly, only personnel authorized by the Principal Investigator will have direct access to the blood storage facilities and samples. As noted previously, the blood samples will not contain the direct identifiers, but will be labeled with a study number and date of blood draw.

References

1. Colombel J, Sandborn W, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with crohn's disease: The CHARM trial. Gastroenterology. 2007;135:52-65.

2. Hanauer S, Feagan B, Lichtenstein G, et al. Maintenance infliximab for crohn's disease: The ACCENT I randomised trial. Lancet. 2002;359:1541-9.

3. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, et al. Vedolizumab as induction and maintenance therapy for crohn's disease. N Engl J Med. 2013 Aug 22;369(8):711-21.

4. Sands BE, Feagan BG, Rutgeerts P, Colombel JF, Sandborn WJ, Sy R, et al. Effects of vedolizumab induction therapy for patients with crohn's disease in whom tumor necrosis factor antagonist treatment had failed. Gastroenterology. 2014 May 21.

5. Feagan B, McDonald J, Panaccione R, et al. Methotrexate in combination with infliximab is no more effective than infliximab alone in patients with crohn's disease. Gastroenterology. 2014;146:681-8.

6. Benchimol E, Seow C, Steinhart A, et al. Traditional corticosteroids for induction of remission in crohn's disease. Cochrane Database Syst Rev. 2008;CD006792.

7. Froslie K, Jahnsen J, Moum B, et al. Mucosal healing in inflammatory bowel disease: Results from a norwegian population-based cohort. Gastroenterology. 2007;133:412-22.

8. Olaison G, Sjodahl R, Tagesson C. Glucocorticoid treatment in ileal crohn's disease: Relief of symptoms but not of endoscopically viewed inflammation. Gut. 1990;31:325-8.

9. Mehandru S, Poles M, Tenner-Racz K, et al. Primary HIV-1 infection in associated with preferential depletion of CD4+T lymphocytes from effector sites in the gastrointestinal tract. J Exp Med. 2004;200:761-70.

10. Panteris V, Haringsma J, Kuipers E. Colonoscopy perforation rate, mechanisms and outcome: From diagnostic to therapeutic colonoscopy. Endoscopy. 2009;41:941-51.

11. Best W, Becktel J, Singleton J, et al. Development of a crohn's disease activity index. national co-operative crohn's disease study. Gastroenterology. 1976;70:439-44.

12. Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for crohn's disease: The SES-CD. . Gastrointest Endosc. 2004;60:505-12.