

1/27/17 Randomized Trial of High Dose vs. Standard Dose Influenza Vaccine in Inflammatory Bowel Disease Patients

1.0 Background

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract which includes Crohn's disease (CD) and ulcerative colitis (UC). ¹ A recent epidemiological investigation estimates that nearly 4 million people worldwide are affected and approximately 1.4 million of these cases occur in the United States. ² IBD can lead to debilitating symptoms, hospitalizations, decreased quality of life, frequent procedures and/or surgery. Treatment options consist of immunosuppressive therapy, such as systemic corticosteroids, immunomodulators (thiopurines and methotrexate) and/or biologics, such as tumor necrosis factor alpha (TNF) agents or an integrin inhibitor, vedolizumab. They can achieve clinical remission and decrease the risk of complications, but also increase the risk for infections, including influenza. ^{3 4}

Influenza is a common respiratory illness that can lead to complications and hospitalizations. Those with chronic medical conditions or who are immunosuppressed, including patients being treated for IBD, are at particularly high risk of complications and mortality from influenza infection. ⁷ Patients with IBD who develop influenza may require hospitalization, including intensive care and interruption of their therapy. Additionally, disease flares have been reported with influenza infection. ⁷ Annual seasonal influenza vaccine is recommended for all IBD patients. However, immunosuppressed IBD patients are at risk of a blunted vaccine response and decreased clinical protection from infection.

Multiple studies have shown lower influenza vaccine responses in patients with IBD compared to healthy individuals; IBD patients treated with TNF agents or combination therapy (TNF inhibitors and immunomodulators) are very likely to mount a poor immune response. ⁸⁻¹⁰

Influenza serum antibody concentration correlates with protection from infection following vaccination. ¹¹ Therefore, increasing influenza antibody responses in patients with IBD would appear to be critical to improving protection from influenza. A high dose (HD) influenza vaccine containing four times more hemagglutinin was licensed based on its ability to induce higher antibody concentrations compared to standard dose (SD) in adults 65 years or older. ¹² Based on this information, we propose the following two specific aims:

Specific Aim #1: Determine whether HD influenza vaccine induces higher antibody concentrations and sustained response in immunosuppressed IBD patients compared to SD. We hypothesize that IBD patients who receive HD influenza vaccine will mount higher antibody concentrations to at least two of the influenza vaccine viruses.

Specific Aim #2: Evaluate the influenza vaccine response in IBD patients treated with vedolizumab, a new gut selective immunosuppressant. We hypothesize that patients on vedolizumab will mount a normal immune response since vedolizumab affects only gut lymphocyte trafficking and does not induce systemic immunosuppression. ¹³

We will test our hypotheses by performing a single center double blind randomized controlled trial in IBD patients receiving influenza vaccination during one season. At the completion of this project, we will have determined the most effective influenza vaccine for immunosuppressed

IBD patients and determine if patients on vedolizumab mount a normal response. This study could provide influenza vaccination protocols for other immunosuppressed populations.

2. Objectives

2.1 Primary Objective

To evaluate if vaccination with HD influenza vaccine induces higher antibody concentration in IBD patients on TNF inhibitors.

2.11 Primary objective aim #1: Antibody response

We will evaluate if the HDIV induces higher antibody concentrations in IBD patients compared to SDIV by comparing the week 3 antibody concentrations between the two groups

Specific aim #2

To evaluate the influenza vaccine response in IBD patients treated with vedolizumab, a new gut selective immunosuppressant

2.12 Primary Objective aim #2: Antibody Response We will compare influenza antibody concentrations after vaccination in patients with IBD treated with vedolizumab to healthy individuals using the 3 week post immunization time point.

2.2 Secondary Objectives

2.21 Secondary outcomes #1 aim #1: Sustained response

A subsequent titer will be done in 6 months post vaccination to assess sustainability of antibody concentration through the season. We will compare antibody concentrations 6 months post vaccination between HD and SD groups and post-immunization to the 6 month post vaccination time point in each group.

2.22 Secondary outcomes #2 aim #1: Vaccine response rates

We will compare seroprotection and seroconversion rates between the HDIV and SDIV groups.

2.23 Secondary outcomes #3 aim #1: Vaccine safety

Study participants will be given a diary card to record symptoms following influenza vaccine administration. We anticipate that the HDIV will cause more injection site reactions¹² than the SDIV but will otherwise be well-tolerated.

2.31 Secondary outcomes #1 Specific aim #2: Sustained response

A subsequent titer will be done in 6 months to assess sustainability of antibody concentration through the season.

2.32 Secondary outcomes #2 Specific aim #2: Vaccine response rates

We will compare seroprotection and seroconversion rates between the vedolizumab treated and healthy groups.

3. Selection of Subjects

The subject population will consist of individuals with inflammatory bowel disease and healthy controls. All IBD patients will meet the inclusion criteria but not the exclusion criteria outlined in the section below:

CASES Specific Aim# 1

3.1 Inclusion Criteria

- 3.11 A history of chronic (greater than 3 month) ulcerative colitis or Crohn's disease diagnosed and *documented by the standard clinical, radiographic, endoscopic and histopathologic criteria.*
- 3.12 Ages 18-64
- 3.13 Currently taking anti-TNF therapy (infliximab, golimumab, adalimumab, or certolizumab) for at least 3 months

3.2 Exclusion Criteria

- 3.21 Received season's influenza vaccine
- 3.22 Allergy to eggs or influenza vaccine
- 3.23 Current use of systemic steroids (oral budenonide and rectal steroids allowed)
- 3.24 Other autoimmune condition(s) (e.g. Rheumatoid arthritis, autoimmune hepatitis)

Specific Aim #2

3.3 Inclusion criteria

- 3.31 A history of chronic (greater than 3 month) ulcerative colitis or Crohn's disease diagnosed and *documented by the standard clinical, radiographic, endoscopic and histopathologic criteria.*
- 3.32 Ages 18-64
- 3.33 Currently on vedolizumab therapy

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3.4 Exclusion Criteria

- 3.41 Received season's influenza vaccine
- 3.42 Allergy to eggs or influenza vaccine
- 3.43 Currently use of systemic steroids (oral budesonide or rectal steroids allowed)
- 3.44 Other autoimmune condition(s) (e.g. Rheumatoid arthritis, autoimmune hepatitis)

Control group

The control group will consist of 20 individuals who meet the following inclusion and exclusion criteria.

Individuals will be obtained from patients without an IBD diagnosis, chronic liver disease, celiac disease or other chronic health condition coming to Digestive Health Center for endoscopic procedures or clinic visits.

3.5 **Inclusion criteria**

- 3.51 Age 18-64
- 3.52 Willing to participate in study

3.6 **Exclusion criteria**

- 3.61 Currently on immunosuppressive therapy
- 3.62 Has a chronic health condition that may have an impact on vaccine antibody concentrations as deemed by the investigators, including chronic liver disease, celiac disease, history of solid organ or bone marrow transplantation.
- 3.63 Older than age 65 years
- 3.64 Patients in whom venipuncture are not feasible due to poor tolerability or lack of easy access.
- 3.65 Vulnerable groups will be excluded from the study (pregnant, lacking consent capacity, Non-english speaking)

3.7 Patient Discontinuation

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Discontinuation is a patient who is enrolled in the study and who terminated from the study prior to completion of study.

The patient is free to withdraw from the study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to terminate a patient's involvement in the study at any time if the patient's clinical condition warrants it. Potential discontinuation criteria for individual patients;

- Adverse Events
- Withdrawal of consent
- Patient is lost to follow-up

4.0 Methods

Specific Aim #1 HD

We plan a randomized controlled trial of HDIV vs. SDIV for IBD patients on TNF monotherapy. Those meeting the inclusion and exclusion criteria will be invited to participate and be randomized.

We will enroll approximately 40 patients and randomized them in a 5:3 fashion to HDIV or SDIV. Subjects who enroll and do not complete 3 week blood draw will be discontinued and another subject will be enrolled. Randomization will generated by a random number generator and investigator will be blinded to randomization scheme.

Both groups will have blood drawn prior to immunization, 3 weeks, and 6 months post vaccination. Participants will be invited to enroll when the seasonal influenza vaccine becomes available, typically about the middle of August until March.

4.1 Control Group

A third group of 20 healthy individuals without IBD, other chronic diseases, or immunosuppressive therapy will be enrolled. All healthy individuals will receive SD influenza vaccine. The influenza vaccine formulation changes annually. Therefore, a measure of response in healthy individuals is necessary in order to rule out any irregularities that may be due to the seasonal vaccine and not IBD or its treatment.

4.2 Vedolizumab group

A prospective study of IBD patients receiving vedolizumab therapy will be conducted. We will enroll approximately 20 patients who are currently on vedolizumab. Subjects who enroll and do not complete 3 week blood draw will be discontinued and another subject will be enrolled. All individuals in this group will receive SDIV and have blood drawn for influenza antibody concentrations prior to immunization, 3 weeks, and 6 months post vaccination.

The study will also be conducted during the influenza season in conjunction with the HDIV study. We will use the healthy control group in the HDIV study to compare the vedolizumab patients.

5.0 PRIOR TO RANDOMIZATION EVALAUTION

5.1 Initial Evaluation

Patients coming to the University of Wisconsin for care of their inflammatory bowel disease will be invited to participate. This will include the Digestive Health Center and UW Infusion Center. A member of their health team will give patients information about the study. The research coordinator will further review information and invite patients to participate in the study.

Patients with UC or CD who meet the inclusion criteria and are in the GI-Hep registry (HSC# 2011-0168) will be invited to participate via re-contact letter (previously IRB approved). The study coordinator will review all the patient information to make sure that the patient qualifies for the study.

5.2 Consent

The patient will be told about the purpose of the study and informed consent will be obtained. Patients 18 years old and older will provide written informed consent prior to randomization.

5.3 Demographic information

Once the patient is enrolled in the study the following information will be collected prior to randomization.

Baseline Data Collected

- a. Age
- b. Sex
- c. Race
- d. Influenza vaccine in prior season (patient report)
- e. Type of Inflammatory Bowel Disease
 - a. Ulcerative Colitis
 - b. Crohns Disease
 - c. Indeterminate Colitis
- f. Type of ulcerative colitis
 - a. Proctitis
 - b. Proctosigmoiditis
 - c. Left sided disease
 - d. Pancolitis
- g. Crohns Subtype per Montreal Criteria (12)
 - a. A1/A2
 - b. L1, L2, L3, L4
 - c. B1, B2, B3
 - d. Perianal disease
- h. Length of disease (as official diagnosis in months.)
- i. Current Medications, doses, and duration
 - a. Mesalamine

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- b. Azathioprine or 6MP
- c. Biologic (infliximab, adalimumab, or certalizumab)
- d. Combination biologic and azathioprine or 6MP
- e. Corticosteroids
- j. Other Comorbid Illness
 - a. Cardiovascular Disease
 - b. Diabetes
 - c. Chronic Obstructive Pulmonary Disease
 - d. Cerebrovascular Disease
 - e. Solid Organ Malignancy
 - f. Leukemia or Lymphoma

The baseline data listed above will be collected by the study coordinator interviewing the subject to get the information and/or collecting this information from the medical record. The demographic data collection sheet will be used.

5.4 Study summary

Start of study.

After all the baseline demographic information is collected the patient will have blood drawn for a serum antibody measurement, randomized to SD or HD, and the influenza vaccine dose will be administered. Patients will also be given a contact phone number to call and discuss any adverse events that might have occurred. Patients will also be provided with an adverse event diary. The diary will allow patients to enter any potential adverse events for 7 days after vaccine administration. The diary will be a paper copy consisting of the adverse events reported in the package insert for influenza vaccine.

Participants will be randomly assigned in a 5:3 fashion to HDIV or SDIV.

Those in the vedolizumab group will not be randomized and will receive SDIV.

5.41 Visit 2

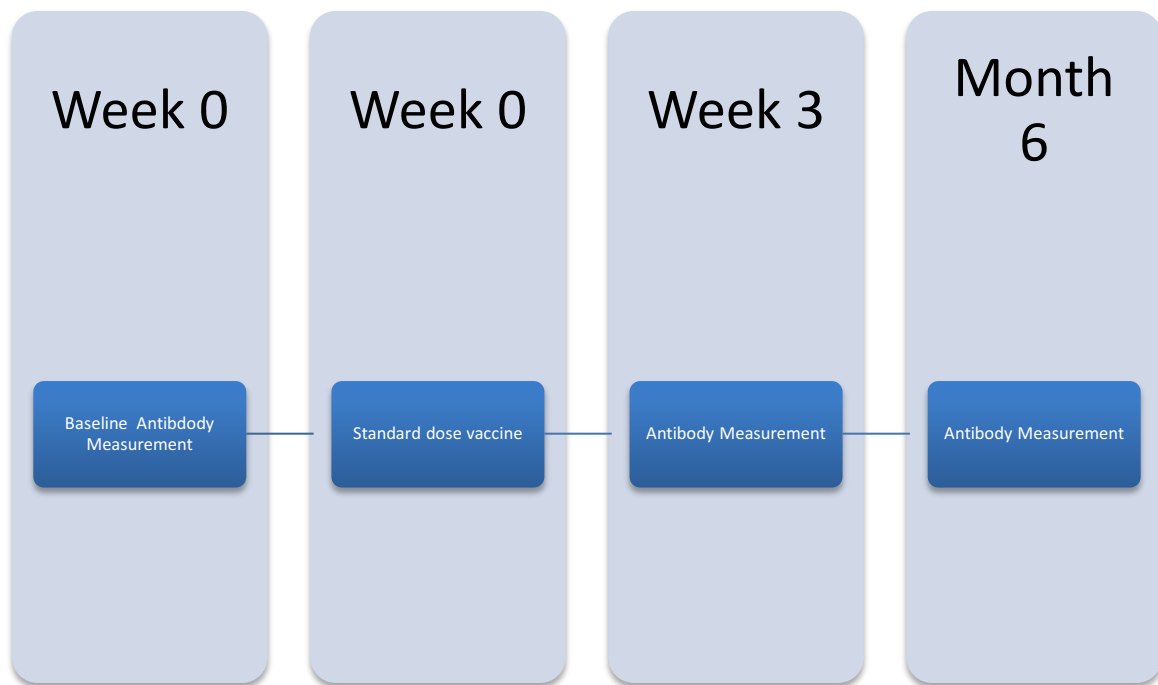
At the 3 week study visit all participants will undergo phlebotomy for post vaccination serum antibody measurement.

5.42 Visit 3

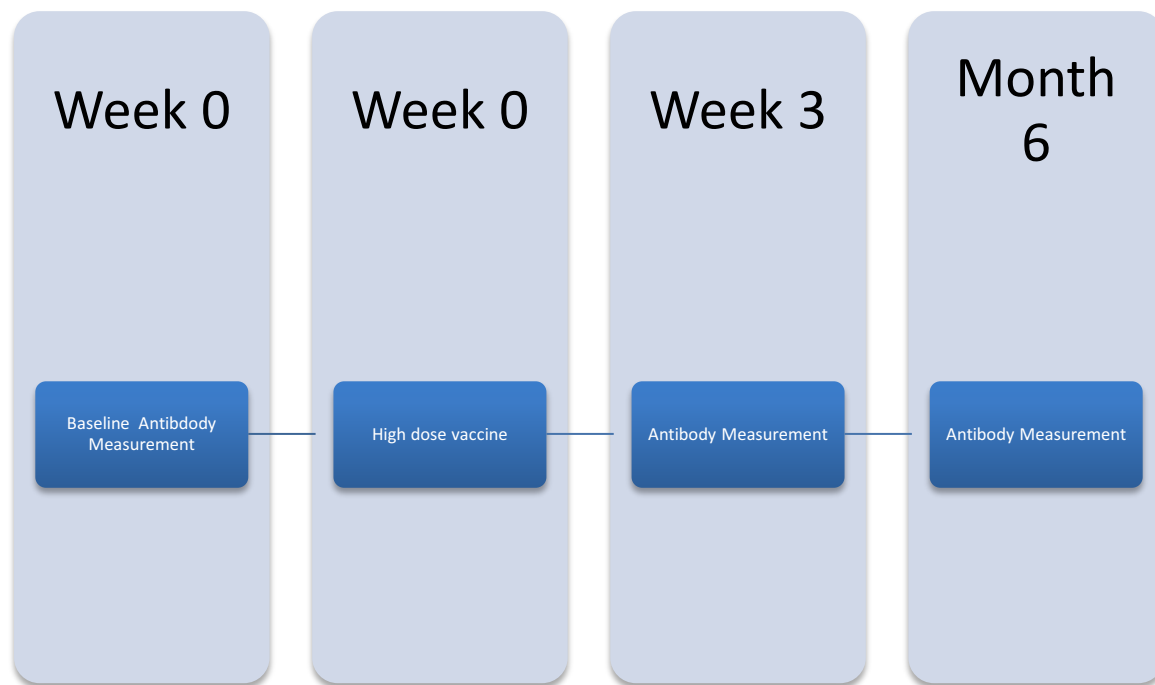
At the 6 month study visit all participants will have phlebotomy for antibody measurement.

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SDIV Group



High Dose Vaccination Group



5.45 Laboratory Assessments

Blood will be collected at week 0, 3, and month 6 in all subjects.

6.0 Randomization

6.1

At the first study visit patients will randomized to the SDIV OR HDIV.

6.2 Randomization

Randomization will occur at week 0.

Randomization will be in a 5:3 ratio based on a random number generator.

7.0 Adverse Events and other Safety aspects

7.1 Definition of Adverse Event

An AE is defined as any untoward medical occurrence in a patient administered either of the vaccines. AE will be recorded after administration of the vaccine and will continue to be recorded for days 0-6 using the adverse event diary. Common adverse events (36) that have been reported in vaccination studies are the following:

- Injection-site pain/soreness/tenderness
- Injection-site swelling/induration
- Injection-site erythema

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- Headache
- Myalgia
- Fatigue
- Muscle pain
- Fever

Participants will be asked about additional adverse events that may have occurred when they return at 3 weeks for a blood draw.

7.2 Definition of Serious Adverse Events

An AE is considered serious if, in the view of the investigator results in any of the following outcomes:

- Inpatient hospitalization
- A life threatening AE (an AE is considered “life threatening” if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death).
- Death

7.3 Reporting of Adverse Events

Adverse events will be reported to the HSC IRB as required and to the Vaccine Adverse Event Reporting System (VAERS). <https://vaers.hhs.gov/index>

7.4 Follow up to Adverse Events

All AEs occurring during the study are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized.

8.0 Measure of effect

8.1 Influenza antibody concentrations

Antibody responses following influenza immunization reach maximum concentrations at 2 to 3 weeks. Studies suggest that antibody levels at 2 and 4 weeks following immunization are indistinguishable.^{27,28} Each individual in the trial will be also categorized as either “Yes” or “No” in terms of seroconversion.^{29,30} All three measures (mean fold increase (MFI) in antibody concentration pre to post-immunization, seroconversion, and seroprotection) for all of each year’s three antigens, will be assessed and statistically analyzed individually.

8.2 Influenza antibody concentration analysis

Hemagglutination inhibition assay (HIA) will be used to measure influenza antibodies. HIA will be performed in duplicate using standard microtiter techniques and serial dilutions. Titrated influenza antigen is incubated with the serum dilutions for 30 minutes. Guinea pig red blood cells (50 µl of 0.5% in phosphate buffered saline) are added and incubated for 45 minutes. The dilution of serum that no longer inhibits hemagglutination is the influenza antibody titer. These

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assays will be performed in Dr. Hayney's laboratory. Her laboratory has substantial experience with these assays.³¹⁻³⁴

9.0 Statistical Plan

9.1 Data Analysis

We will compare geometric mean antibody concentrations and mean fold increase in antibody concentrations between groups using t-tests. Seroprotection rates between the groups, defined as an antibody titer of at least 1:40 and rates of seroconversion, defined as having a fourfold increase in antibody concentrations following immunization, will be compared using chi square tests or Fisher's exact tests.

9.2 Power Calculation

Forty individuals will be enrolled in the study in a five high dose to three standard dose vaccine ratio. This strategy yields 89% power to detect an A/H3N2 antibody concentration of 80 hemagglutination inhibition units, which is higher than that reported in patients with IBD treated with TNF based therapy who received SDIV.²⁶ The power to detect differences in A/H1N1 influenza antibody concentrations is greater than 90%. However, this sample size yields only a 60% power to detect the similar difference between groups. The likely reason for this low power is that the study upon which we are basing our sample size calculations showed a GMT of 98 for influenza B. It is unrealistic to hypothesize that we can push it much higher, even with HDIV.

10. Lab Specimens and Future Research

After we have performed the tests we plan to perform for this study, we will keep any leftover blood and use it in future research projects. Data created from the subjects' participation in this study will also be stored. This will be stored and locked in the GI Research Office. Although the specific research using your specimens is not known, the research will be related to the study of IBD and/or vaccine-related research. Banking of these samples is required for participation, and not optional. Dr. Caldera and the GI Research Office staff will have access to the codes links. If subjects no longer wish for their sample to be stored they can contact Dr. Caldera or the research office and the specimens will be disposed of according to standard medical research procedures. If subjects do not make such a request, the specimen will be stored indefinitely.

Specimens will be labeled with the subjects study ID number and date of collection so that data collected for this protocol can be linked to the sample. Samples will be stored in Rennebohm Hall at the University of Wisconsin. Only investigators and key personnel assigned to the laboratory have access to the lab. Samples will be coded (labeled with subject ID and date of collection) before they arrive to the lab. All computers used for data storage and analysis are password protected and used exclusively by key personnel.

Any future studies that will use these specimens will be done by UW researchers and will be submitted for a separate IRB approval. Only coded samples and data will be released for future research. The information linking the samples and data to individual subjects will not be released.

11. Drugs/ Vaccines

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11.1 High Dose Influenza

A high dose (HD) influenza vaccine containing four times more hemagglutinin was licensed based on its ability to induce higher antibody concentrations compared to standard dose (SD) in adults 65 years or older (Fluzone High-Dose) trade name. Patients on TNF inhibitors will be randomized to this arm of the study.

11.2 Quadrivalent vaccine

Standard dose flu vaccine (Fluzone Quadrivalent) will be used in the vedolizumab arm, control and TNF inhibitors not receiving high dose.

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