A Pilot Study to Evaluate if Response to Infliximab or Adalimumab May be Regained with the Addition of an Immunomodulator

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Background

The immunogenicity of anti-tumor necrosis factor alpha (anti-TNF) therapy in inflammatory bowel disease (IBD) is an important cause of loss of response to therapy that may lead to escalation of dose or discontinuation of therapy. Antibodies may develop to infliximab (ATI) or to adalimumab (ATA) and cause this loss of response, also known as a secondary loss of response. In an attempt to overcome these antibodies, dose escalation can be accomplished either by increasing the dose or shortening the interval between doses. The ability of dose escalation to overcome loss of response due to the presence of ATI or ATA remains controversial. Escalation of dose increases the cost of therapy substantially. If the decision is made to discontinue therapy after a secondary loss of response, a clinician may choose to switch to an alternate anti-TNF therapy of which there are currently only four. Loss of response to one agent predicts a lesser response to other anti-TNF agents and with a limited number of therapeutic options the goal should be to optimize therapy rather than to discontinue therapy.

An alternative approach is the addition of immunomodulator (IM) therapy to counteract the antibody response and regain efficacy of the biologic medication. Three such IMs known to be effective in the treatment of IBD are azathioprine (AZA), 6-mercaptopurine (6MP) and methotrexate (MTX). The SONIC trial showed that patients on infliximab and azathioprine only developed antibodies at 4% of the time as opposed to those on infliximab monotherapy who formed ATI at 13%. The same principal was shown during the COMMIT trial in which patients on infliximab alone had ATI at a rate of 20% versus 4% on methotrexate plus infliximab. Ben-Horin et al. reported five patients treated initially with infliximab monotherapy whom had secondary loss of response based on clinical symptoms. These patients had ATI and all had undetectable troughs of infliximab. In all five patients ATI became undetectable, an adequate trough level was restored and the patients regained clinical response with the addition of an immunomodulator. Combination therapy with azathioprine and infliximab has led to a higher percentage of patients in steroid free remission than either drug alone. Our goal is to treat patients' who have lost response to adalimumab or infliximab with an immunomodulator with the goal of eliminating the circulating antibodies to the anti-TNF and restoring efficacy.

Specific Aims/Hypotheses

Hypotheses :

In patients with loss of response to infliximab or adalimumab who also have detectable ATI or ATA and inadequate trough levels of drug, addition of IM will:
1) improve clinical response, restore trough levels of drug and cause a reduction or resolution of ATI or ATA.
2) normalize inflammatory markers including sedimentation rate, C-reactive protein (CRP) and/or fecal calprotectin.
3) improve or heal mucosal inflammation.

Aims :

Primary: To determine if addition of an IM to anti-TNF, either infliximab or adalimumab, in those patients with Crohn's Disease (CD) or Ulcerative Colitis (UC) who have a secondary loss of response to anti-TNF with measurable ATI or ATA and inadequate anti-TNF trough levels:

- Will improve clinical response
- Will restore adequate trough levels of anti-TNF and eliminate or reduce ATI or ATA

Secondary: To determine if addition of an IM to anti-TNF, either infliximab or adalimumab, in those patients with CD or UC who have a secondary loss of response to anti-TNF with measurable ATI or ATA and inadequate anti-TNF trough levels:

- Will improve or heal endoscopic appearance of the mucosa
- Will improve or normalize serologic and fecal markers of inflammation

Inclusion/Exclusion Criteria

- Study Subjects
  - Inclusion Criteria
    - Patients with inflammatory bowel disease who on are stable doses of infliximab or adalimumab for at least 3 months who experience a secondary loss of response to the medication based on clinical symptoms.
    - Presence of at least one objective marker of active disease: active disease based on endoscopy, elevated fecal calprotectin or serologic markers of inflammation (C-reactive protein or sedimentation rate).
    - Crohn's patients have a Harvey Bradshaw index ≥ 5
    - Ulcerative colitis patients have a Ulcerative Colitis Clinical Score ≥ 5
    - Have adetectable ATI or ADA.
    - Oral corticosteroid therapy is allowed. (prednisone at a stable dose ≤ 30 mg/day, budesonide at a stable dose ≤ 9 mg/day, or equivalent steroid) provided that the dose has been stable for the 4 weeks immediately prior to enrollment if corticosteroids have recently been initiated
  - Exclusion Criteria
    - Previous noncompliant with medications
    - < 18 years of age or >80 years of age.
    - Congestive heart failure
    - Abnormal liver tests alanine aminotransferase (ALT) or aspartate aminotransferase (AST) 2 × the upper limit of normal (ULN) or leucopenia WBC count <3 × 109/L
    - Pregnant or planning on becoming pregnant.
    - Active tuberculosis or hepatitis B infection
    - Any cancer within the past 5 years. (Exception non-melanomatous skin cancer.)
    - Receiving any immunomodulator therapy within the past 3 months
    - Evidence of or treatment for *C. difficile* infection within 60 days or other intestinal pathogen within 30 days prior to enrollment
    - Clinically significant extra-intestinal infection (e.g., pneumonia, pyelonephritis) within 30 days of the initial screening visit
    - Any live vaccinations within 30 days prior to study drug administration except for the influenza vaccine
    - Any identified congenital or acquired immunodeficiency (e.g., common variable immunodeficiency, human immunodeficiency virus [HIV] infection, organ transplantation)
    - Any unstable or uncontrolled cardiovascular, pulmonary, hepatic, renal, endocrine/metabolic, or other medical disorder that, in the opinion of the investigator, would confound the study results or compromise patient safety
    - Unable to give own informed consent

Study Protocol

- **Screening and Enrollment**
  - Twenty patients will be recruited from the IUHP IBD clinic or at the time of ileo-colonoscopy. Patients with a history of CD or UC on a stable dose of infliximab or

adalimumab for 3 months, but with active symptoms (as determined by an expert in IBD) and with objective evidence of active disease with either elevated serologic or fecal markers of inflammation or endoscopic evidence of active disease will be eligible for enrollment as long as they also have measurable ATI (>3.1) or ATA (>1.7) and lack other exclusion criteria.

- Informed consent will be obtained from Study Subjects.
- Subjects if enrolled with have a baseline visit and a follow-up visit at 4 months.
- We will add an IM to their current biologic therapy following standard care and clinical practice. IM's are used in patients who are having ongoing symptoms despite current therapy or lost response to their monotherapy. The choice of IM therapy (azathioprine, 6 mercaptopurine or methotrexate) will be individualized for each patient based on prior use and history of known side effects. Our first line choice based on prior studies will be to use 6 mercaptopurine (1-1.5 mg/kg dosing) or azathioprine (2.5 mg/kg dosing). We will check TPMT (thiopurine methyltransferase) levels and patient has inadequate levels we will use methotrexate. If a patient had side effects to one class of drug the alternative will be chosen. If patients are heterozygotic for TPMT then we will use half dose of the AZA/6 MP or can use methotrexate. The dosing of the methotrexate will be 25 mg subcutaneously weekly with weekly folic acid 5 mg the day after the methotrexate. If subcutaneous administration is not tolerated oral methotrexate can be used.
- Patients will remain on same dose of infliximab or adalimumab for entirety of the study and no changes of dosing interval will be allowed.

- Baseline Visit
  - Demographic Data
    - Gender, age, weight, height, ethnicity, duration of disease

  - Blood work - We will measure: complete blood count, comprehensive metabolic panel, C - reactive protein, sedimentation rate. Pregnancy test for all females of child bearing age. Stool will be checked for inflammation with fecal calprotectin and infection with clostridium difficile PCR toxin. We will check a TPMT level prior to initiating AZA or 6MP.

- Baseline and Follow-up visit Clinical History and Symptoms: The following questionnaires are routinely administered to all patients at every clinic visit in our IBD clinic to monitor symptoms and quality of life.
  - Harvey Bradshaw Index for patients with Crohn's disease
  - Ulcerative Colitis Clinical Score for patients with Ulcerative colitis
  - Short Inflammatory Bowel Disease Questionnaire for all patients. Quality of life scale.

- <u>Standard-of-Care Procedures at baseline and follow-up visit at 4 months for Study Subjects:</u>
  - Ileo-colonoscopy
    - Ileo-colonoscopy at baseline and follow-up examination
      - For patient <u>*not responding to therapy as determined by their treating gastroenterologist under good clinical care*</u> we perform an endoscopic examination prior to changing therapy. The endoscopy determines if the patient's symptoms are related to active disease, the severity of the disease if active or if normal and another cause of their symptoms should be evaluated.

        - After administering a new therapy, it is acceptable and standard care to perform a colonoscopy to assess treatment response 4 months after the initiation.
        - For those without colonic or terminal ileum disease we will not perform a colonoscopy during the study period.
    - During the ileo-colonoscopy mucosal biopsies are taken routinely from abnormal areas. This is done under standard practice and care to examine the histological activity of their disease. Histology is reported by our pathologists as inactive or active with mild, moderate or severe activity.
    - Endoscopic activity will be graded by the gastroenterologist using the Simple endoscopy score-Crohn's disease (SES-CD) or the Mayo endoscopic subscale for ulcerative colitis.
- Serum sample standard care while taking one of the above IM's.
    - Follow-up Labs:
        - Total WBC and lymphocyte counts will be regularly monitored for all patients. Azathioprine, 6-mercaptopurine, or methotrexate must be discontinued, if applicable, for a confirmed absolute lymphocyte count $<0.5 \times 109/L$. For an absolute lymphocyte count $<0.5 \times 109/L$, the hematology must be repeated in 2 weeks. WBC and lymphocyte counts will be followed for these patients until they return to an acceptable level.
        - Protocol for azathioprine/6-mercaptopurine initiation of WBC monitoring will be weekly for 1 month, every 2 weeks for 1 month, 1 month later then every 3 months as we do in standard practice. WBC will be checked one month after initiation of methotrexate and then every 2 months as we do in standard practice.

        - Liver tests will be checked one month after starting methotrexate and then every 2 months as we do in standard clinical practice. Liver tests will be checked 1 month after starting azathioprine/6-mercaptopurine. Then every 3 months per standard clinical practice. If ALT/AST in patients on methotrexate is $\geq$2 Upper limit of normal the medication will be discontinued. If ALT/AST rise in patients on azathioprine/6 MP the dose should be lowered and liver tests followed every week until normalization. Clinicians can check metabolites (6-thioguanine and 6-methylmercaptopurine) to help guide dosing as done in standard practice. If liver tests fail to normalize with the above changes the medication will be stopped.

        - C-reactive protein and sedimentation rate will be checked again at 4 months at the follow-up visit. In addition, we will check an infliximab or adalimumab trough level and ATI or ADA at this visit. At the 4 month visit we will check AZA/6MP metabolites (6-thioguanine and 6-methylmercaptopurine).

- Stool samples
    - At baseline we will check a clostridium difficile PCR of their stool and a fecal calprotectin to assess for active inflammation
    - At follow-up visit all patients will give a stool sample to recheck fecal calprotectin.

Outcomes

- Primary Outcomes
    - 1. To determine if patients with secondary loss of response with infliximab or adalimumab can regain clinical response with the addition of an immunomodulator: azathioprine, 6-mercaptopurine or methotrexate.
        - Endpoint: Change in HBI score, with improvement defined as a decrease in ≥3 points or remission HBI score of <5
        - Endpoint: Change in UCCS with improvement defines as a decrease in ≥3 points or remission with score < 5
        - Endpoint: Change in SIBDQ quality of life score
    - 2. To evaluate if the addition of immunomodulator therapy eliminates ATI or ADA below accepted thresholds and increase trough levels of infliximab or adalimumab
        - Endpoint: . Threshold levels for ATI is < 3.1and is < 1.7 for ADA.

- Secondary Outcome
    - 1. To evaluate endoscopic improvement and mucosal healing from baseline to follow-up after the addition of an immunomodulator to infliximab or adalimumab.
        - Endpoint: Improvement or normalization of Mayo Endoscopy Score for UC patients. (scored 0-3) A score of 0 or 1 equivalent to mucosal healing. Improvement or normalization of the Simple Endoscopic Score-Crohn's Disease (SES-CD). Score is 0-15 with 0 indicating mucosal healing.
    - 2. To evaluate if addition of an immunomodulator to infliximab or adalimumab results in improvement of serologic and fecal markers of inflammation
        - Endpoint: Improvement or normalization of C - reactive protein, sedimentation rate and fecal calprotectin from baseline to follow-up visits.

Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Any adverse events or unanticipated problems involving risk to participants or others will be reported to the Institutional Review Board. Physicians will perform adequate work-up and care until event resolves.

Study Withdrawal/Discontinuation

Patient can withdraw from the study at any time without compromising future care.

Follow-up and Record Retention

Patients will continue to follow-up with their gastroenterologist for regular care after the completion of the study. Their records will be in our medical record system: Cerner.

Statistics

Correlation kappa statistics, chi square, analysis of variances will be used. Wilcoxon rank sum test for non-parametric comparison of before-after values for CRP, ESR pre- vs. post immunomodulator treatment.

Appendix

Simple Endoscopic Score for Crohn's Disease

	Simple Endoscopic Score for Crohn's Disease values			
Variable	**0**	**1**	**2**	**3**
Size of ulcers	None	Aphthous ulcers	Large ulcers	Very large ulcers
		(Ø 0.1 to 0.5 cm)	(Ø 0.5 to 2 cm)	(Ø >2 cm)
Ulcerated surface	None	<10%	10-30%	>30%
Affected surface	Unaffected segment	<50%	50-75%	>75%
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

Mayo Endoscopy Subscale

Findings of flexible procto-sigmoidoscopy or colonoscopy
0= Normal or inactive
1= Mild disease (erythema, decreased vascular pattern, mild friability)
2= Moderate (marked erythema, abscent vascular pattern, friability, erosions)
3= Severe disease (spontaneous bleeding, ulceration)

THE INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (SIBDQ)

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. You will be asked about symptoms you are having as a result of your inflammatory bowel disease, the way you have been feeling in general, and how you mood has been.

- **How often is the feeling of fatigue or being tired and worn out been a problem for you during the last 2 weeks?**

All of the time Most of the time A good bit of time Some of the time

A little of the time Hardly any time Never

- **How often during the last 2 weeks have you had to delay or cancel a social engagement because of you bowel problems?**

All of the time Most of the time A good bit of time Some of the time

A little of the time Hardly any time Never

- **How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you have liked to have done over the last 2 weeks?**

All of the time Most of the time A good bit of time Some of the time

A little of the time Hardly any time Never

- **How often during the last 2 weeks have you been troubled by pain in the abdomen?**

All of the time Most of the time A good bit of time Some of the time A little of the time Hardly any time Never

- **How often during the last 2 weeks have you felt depressed or discouraged?**

All of the time Most of the time A good bit of time Some of the time

A little of the time Hardly any time Never

- **How much of a problem have you had passing large amounts of gas, in the last 2 weeks?**

All of the time Most of the time A good bit of time Some of the time

A little of the time Hardly any time Never

- **Overall, in the last 2 weeks, how much of a problem have you had maintaining or getting to the weight you would like to be?**

All of the time Most of the time A good bit of time Some of the time

A little of the time Hardly any time Never

- **How often, during the last 2 weeks, have you felt relaxed or free of tension?**

All of the time Most of the time A good bit of time Some of the time

A little of the time Hardly any time Never

- **How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the toilet even though your bowels were empty?**

All of the time Most of the time A good bit of time Some of the time

A little of the time Hardly any time Never

- **How much of the time, during the last 2 weeks, have you felt angry as a result of your bowel problems?**

All of the time Most of the time A good bit of time Some of the time

A little of the time Hardly any time Never

Harvey Bradshaw Index (HBI)

- **How did you feel overall last week?**

Very well	Slightly sub-par	Poor	Very poor	Terrible
0	1	2	3	4

- **Do you have pain in your stomach?**

Very well	Slightly sub-par	Poor	Very poor	Terrible
0	1	2	3	4

- **How many liquid bowel movements have you had, on average, per day over the last week?**

  _____ / day

- **Do you have an actively draining fistula/pus at the anus?** Yes No
- **Do you have swollen, tender, stiff joints?** Yes No
- **Do you have pain and redness, inflammation in the eyes?** Yes No
- **Do you have ulcers in the mouth or on your skin or tender rashes?** Yes No

MD only below this line:

- **Abdominal mass**

None	Dubious	Definite	Definite and Tender
0	1	2	3

- **Complications (score 1/item)**
  - Erythema nodosum, arthralgia, uveitis, aphthous ulcers, pyoderma
  - Anal fissure or active fistula, abscess

Scoring

<5 remission

5-7 mild disease

8-16 moderate disease

>16 severe disease

ULCERATIVE COLITIS ACTIVITY SCORE (UCCS)

- **How many loose bowel movements per day have you had, on average, during the last week?**

None	1-2 over normal	3-4 over normal	5 or more over normal
0	1	2	3

- **Do you see blood in the stool?**

No 0 | Streaks, sometimes 1 | Obvious blood, most times 2 | Frank blood by itself 3

- **Do you have pain in your stomach/abdomen?**

  No 0 | Mild 1 | Moderate 2 | Severe 3

- **How did you feel in general last week?**

  Generally well 0 | Fair 1 | Poor 2 | Terrible 3

- **Do you have swollen, tender, stiff joints?** Yes No
- **Do you have pain and redness, inflammation in the eyes?** Yes No
- **Do you have ulcers in the mouth or on your skin or tender rashes?** Yes No

MD only below this line:

- **Global assessment:**

  Quiescent 0 | Mild 1 | Moderate 2 | Severe 3

Study Visit Schedule									
Labs/Tests	Screening	Baseline	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 16
CBC		x	x	x	x	x	x	x	x
BMP		x							x
LFTs		x		x		x		x	x
ESR		x							x
CRP		x							x
TPMT	x	x							
Infliximab Trough	x								x
Anti-Drug Antibody Infliximab	x								x
Urine pregnancy test	x								
C diff toxin PCR		x							
Fecal Calprotectin		x							x
Colonscopy		x							x
Terminal Ileum Mucosal Biopsy		x							x
Colon Mucosal Biopsy		x							x
HBI		x							x
SIBDQ		x							x
May Subscale Endoscopy		x							x
SES-CD		x							x
UCCS		x							x
thiopurine metabolites									x
* If on methotrexate, will repeat CBC/LFTs weeks 4,8, and 16									