Correlation of Infliximab levels with Outcomes in Ulcerative Colitis

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General Study Information

Principal Investigator/ sponsor investigator: Darrell S. Pardi

Study Title: Correlation of Infliximab levels with Outcomes in Ulcerative colitis

Protocol version number and date: Version #3 Thursday, March 17, 2016

List of Abbreviations: TNF (Tumor Necrosis Factor), CRP (C-reactive protein), ESR (Erythrocyte Sedimentation Rate), CMV (Cytomegalovirus) and complete blood cell (CBC)

Research Team, and Study site:

Sponsor Investigator: Darrell S. Pardi, M.D.

Co-Investigator/Fellow: P. Grace Dosanjh, M.D., **Dr. Michael Van Nordstand,**

Study Coordinator: Patricia P. Kammer

Site: Division of Gastroenterology and Hepatology;

Mayo Clinic

200 First Street, SW

Rochester, Minnesota, U.S.A, 55905

Corresponding author:
Darrell S. Pardi, MD, MS
Professor of Medicine
200 First Street SW
Rochester, MN 55905
E-mail: pardi.darrell@mayo.edu
Phone: (507) 284-2407
Fax: (507) 284-0538

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Purpose

Hypothesis:

We hypothesize that non responders to infliximab will have lower early drug levels then responders thus reflecting an increased risk of colectomy. Additionally, we will estimate an optimal day 4 level based on the study results.

Aims, purpose, or objectives:

Summary

There is increasing interest in the pharmacokinetics of biologics such as Infliximab and their clinical relevance. In this study we propose to measure infliximab levels during the first week after infusion in adult patients hospitalized with severe ulcerative colitis (UC). We will compare those infliximab levels with one and three month outcomes including the requirement for colectomy, changes in inflammatory markers, and complications such as intercurrent infections and cardiac, renal, or respiratory deterioration

Background and Significance

Ulcerative colitis is a chronic inflammatory bowel with significant associated morbidity and risk of colectomy.[1] . Although many environmental risk factors including smoking, medications, childhood hygiene, and infections have been implicated and studied, none can fully explain the disease pathogenesis.[2] Additionally, genetic susceptibility and a complex interplay between the microbiome and the immune system likely lead to the development of this inflammatory bowel disease.[3]

Acute and chronic complications associated with UC include severe bleeding, toxic megacolon, infection and colorectal cancer. Hospitalized patients with a flare of moderate- to-severe ulcerative colitis can be especially difficult to manage if they do not respond to intravenous corticosteroids. At this point, medical therapy or a total proctocolectomy with a two or three stage ileal pouch–anal anastomosis (IPAA) is frequently considered. [4] Treatment with cyclosporine may only delay colectomy in most patients.[5] Additionally, cyclosporine carries a substantial risk of toxicity. [6] Increasingly, Infliximab, a TNF alpha inhibitor, is being used a rescue therapy in this situation. [7]

. Infliximab is approved for induction and maintenance of clinical remission and mucosal healing in patients with moderate to severe active ulcerative colitis, in those who have an inadequate response to conventional therapy such as IV steroids. It is typically dosed at 5 mg/kg at 0, 2, and 6 weeks, followed by 5 mg/kg every 8 weeks thereafter The alternative to rescue medical therapy with infliximab is proctocolectomy with ileal pouch anastomosis, which carries risks including pouchitis, fecal incontinence, pouch failure requiring further surgical procedures and female infertility [8] [9, 10] or proctocolectomy with permanent end-ileostomy, which many patients wish to avoid. An induction regimen of 3 doses of Infliximab followed by a maintenance dose every 8 weeks is used to achieve response in hopes of avoiding colectomy. [11] Unfortunately, a large proportion of patients are unable to achieve (primary failure, approximately 30%) or sustain a clinical response over time (up to 50%, secondary failure) [12] and end up getting a colectomy.". [12]

Potential implicated pathways in non-responders include fecal wasting of infliximab [13] and factors that accelerate drug clearance such as a large TNF or CRP burden, anti-infliximab antibodies (ATI), low serum albumin, male sex and larger body size. [14] Patients with severe ulcerative colitis who fail corticosteroids and standard dosing with infliximab usually proceed to proctocolectomy. Optimizing infliximab blood levels in patients with moderate-

severe ulcerative colitis would improve the efficacy and further reduce the need for colectomy. However, there is a paucity in the literature as this is a relatively new school of thought. Our study will address this deficit by evaluating the relationship between early drug levels of infliximab in ulcerative colitis and colectomy rates at one and three months.

Specific Aims

Primary Aim

The primary aim of this study is to analyze the relationship between daily infliximab levels and colectomy free survival at 1 and 3 months. We hypothesize that non responders will have lower early drug levels and correlate with increased colectomy rates. Based on the resulting correlations, we will estimate an optimal drug level to improve clinical outcomes and provide data to support future research. If our hypothesis is correct, we intend to pursue a second study which will be randomized and involve early infliximab dose stacking (weeks 0 and 1) in patients with suboptimal infliximab levels vs standard infliximab administration (weeks 0, 2, 6) to see if the risk of colectomy can be decreased.

Secondary Aims

The secondary aims of this study are to assess relationships between colectomy and other potential biomarkers

Subject Information – charts, records, images, or specimens are considered 'subjects'

Target accrual is the proposed number of subjects to be included in your study at your site. "Subjects" may include Mayo Clinic charts, records, or specimens, ***and/or*** *charts, records, or specimens received at Mayo Clinic from external sources for collaborating analysis by the investigator under this IRB application*:

Target accrual: 25

Subject population: Patients must be scheduled to receive clinically indicated infliximab at the discretion of their treating physician during an acute hospitalization with a flare of moderate to severe UC. The study will enroll a total of 25 subjects."

Inclusion Criteria:

1. Adults, ages >18
2. Hospitalized, with a moderate-sever flare of Ulcerativa Colitis, based on the Mayo Scoring System for Assessment of UC. Mayo score activity score of equal or greater than 6g
3. Treatment naïve to anti TNF agents
4. Initiation of infliximab, with or without immunomodulator such as Azathiorpine.
5. Ongoing use of immunomodulators such as azathioprine or 6MP is acceptable. Their initiation or continuation remains at the discretion of the treating physician

Exclusion Criteria

1. Ongoing or prior treatment with Infliximab or other anti TNF agents
2. Ongoing or recent (within 1 month) administration of rescue cyclosporine
    a. Concomitant immunomodulator therapy is acceptable if on stable dosing for at least 4 weeks
    b. Current medications may be continued at the discretion of the treating physician
3. Fulminant colitis requiring emergent surgery or toxic megacolon
4. Pregnancy
5. Infectious colitis, example Clostridium difficile or CMV colitis
6. Active infection or abscess
7. Untreated latent or active tuberculosis (TB). Those with latent TB who are currently undergoing treatment can be included. Please refer to appendix 1 for more information on specific inclusion and exclusion criteria related to TB testing. Refer to 1.4.2 of appendix 1 for TB screening questions
8. Active malignancy
9. Active or history of Congestive Heart failure (CHF) or those who have received treatment for CHF
10. Active or history of Multiple Sclerosis (MS), or those who have received treatment for MS
11. Prisoners, institutionalized individuals, and individuals who are not capable of giving informed consent
12. Judgement of investigator

Will a Certificate of Confidentiality be obtained? NO.

Study Design

Methods:

Design

We propose an open label pilot study of 25 adult moderate-severe ulcerative colitis inpatients. Since existing literature on our study hypothesis is scarce, this sample size was chosen based on other pilot studies of biologic therapies in patients with IBD.

Study Population

Included patients must be receiving clinically indicated infliximab at the discretion of their treating physician during an acute hospitalization with a flare of moderate to severe UC. We recognize that our patient population will include referral amongst those from the local Olmsted County and surrounding areas.

To identify subjects, the inpatient gastroenterology service list at St Mary's Hospital in Rochester Minnesota will be reviewed daily. Patients will also be enrolled from any Mayo Clinic Health System (MCHS) site LaCrosse, if they meet the inclusion and exclusion criteria and are under the care of Mayo gastroenterologist. To capture those on the internal medicine service, the gastroenterology consult service list will also be reviewed daily. As these patients will be admitted with a suspected IBD flare, a clinically indicated colonoscopy or flexible sigmoidoscopy will have been completed with colon, terminal ileum and/or sigmoid colon biopsies. Endoscopic findings will be noted and

those deemed to have moderate to severe disease activity will be included based on the Mayo Scoring System for Assessment of Ulcerative Colitis Activity will be considered. Subject will participate for a maximum of 3-months and will complete the study when the 3-month follow-up phone call is completed.". *Informed Consent Process*

A member of the study staff will meet with the potential participant with the assent of the hospitalist who is in charge of the patient's care. The study will be explained to the potential subject and the risks and benefits will be discussed the potential subject will be given an opportunity to ask questions. Only subjects who agree and sign an informed consent document will be included in this study. A copy of the written consent document will be provided to the potential participant. "Infliximab doses and frequency of administration will be at the discretion of the treating physician."

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Schedule of events

Study procedure	Enrollment visit	Study day 1	Study day 2	Study day 3	Study day 4	Study day 5	Study day 6	Study day 7	1 month Phone call	3 month phone call
Informed consent	x									
Demographics	x									
Medical History	x									
Inclusion/exclusion criteria including confirmation of appropriate TB screening	x									
Concomitant meds	x	x	x	x	x	x	x	x	x	x
Study stool labs*		x	x	x	x	x	x	x		
Study blood labs*		x	x	x	x	x	x	x		
Study Questionnaire		x	x	x	x	x	x	x	x	x
Adverse events/ SAE		x	x	x	x	x	x	x	x	x

***Study labs include CBC with differential, Sedimentation rate, C reactive protein, Creatinine, TNF level, Albumin, Fecal Calprotectin Infliximab and antibody to infliximab levels. Blood and stool to research lab.**

Data Collection

As part of the study, subjects will complete a daily questionnaire of clinical symptoms including stool counts, presence of blood or mucous, number of nocturnal bowel movements, fever, malaise, weight loss, urgency or tenesmus and abdominal pain[3]. Estimated time to complete a questionnaire is 5 minutes Additionally stool and blood laboratory data such as CBC with differential, creatinine, TNF levels, albumin, fecal calprotectin, ESR, CRP, infliximab and antibodies to infliximab levels will be obtained daily for a week, following week 0 Infliximab infusion. If any of these labs has been performed on the given day for a clinical indication or to guide management by the treating physician, they will not be repeated. If a subject undergoes colectomy within the first 7 days of the study we will stop collecting lab data from them.

All samples collected for the study will be deidentified. Sample labels will contain only subjects study ID, visit # and date of collection. Lab test will be requested by the study physician using Mayo standard of practice

procedure. Samples will be collected, processed and sent to the lab per Biospecimens Accessioning and Processing (BAP) department at Mayo Clinic. They will be aliquoted per testing instructions and delivered to the appropriate lab for analysis.

Those subjects who are discharged prior to a week's time will have blood and stool collected as outpatients at the Mayo Clinic outpatient lab area. Similarly, subjects will receive the rest of daily questionnaires and self-addressed envelopes Subjects that are unable to return to Mayo Clinic, will receive mail in blood and stool kits that can be mailed to the Mayo Clinic lab at the time of discharge. They will be provided instructions regarding venipuncture at outside labs, stool sample collection and shipping of samples. The subjects will be given addressed and postage paid mail in kits. They will not be responsible for venipuncture or shipping cost. Subjects will receive remuneration of $25.00 if they complete the study or a pro-rated portion of that amount if they complete only a part of the study. Subjects will receive a follow up phone call at 1 and 3 months after Inflixambe intitation (+/- 5 days). A followup symptom questionnaire also will be completed at these phone calls. to gather information about progression of symptoms. In an effort to minimize any potential risks to subjects, all information will be treated in accordance with Mayo Clinic patient confidentiality rules and regulations as well as with HIPAA regulations. Samples will be destroyed at the end of the study."

Endpoints

Primary Endpoint:

1. Colectomy free survival at 1 and 3 month

Secondary Endpoints:

1. Improvement in variables such as ESR, CRP, TNF levels, hemoglobin and stool counts

Estimated Timeline

Final protocol to IRB approval: 1 month

IRB approval to First Patient, First Visit: 1 month

First Patient, First Visit to Last Patient, Last Visit: 18 months

Treatment period: 3 months from date of Remicade initiation

Final study report timing after Last Patient, Last Visit: 2 months

Publication submission timing after final study report: 2 months

Safety Events

Safety events during the course of the study will be monitored. Adverse events will be monitored from date of Remicade initiation until the 1 month follow up phone call and serious adverse events will be monitored from date

of Remicade initiation until the 3 month follow up phone call. Please refer to appendix 2 for protocol adverse event language for investigator-initiated studies."

Check all that apply. If none apply, leave blank:

☐ This is a multisite study involving Mayo Clinic and non-Mayo Clinic sites.
When checked, describe the research procedures/activities being conducted **only** at Mayo Clinic:

☐ Mayo Clinic staff will be engaged in research activity at a non-Mayo Clinic site. *When checked, provide the location and a detailed description of the Mayo Clinic research staff involvement*.

☐ This study is to establish and/or maintain an ongoing database or registry for research purposes only.

x The research involves contact or interaction with subjects, for example, surveys, questionnaires, observation, blood draw. **The study will involve daily blood draws for seven days. We understand this is more draws then normally associated with a minimal risk study. Most of the subjects will be hospitalized, with daily blood draws, we will not repeat any testing done clinically. This is why we feel it the study still meets the minimal risk category.**

☐ The study involves photographing, audiotaping or videotaping subjects (and guests).

Blood Collection

If this study involves prospective blood collection by finger, heel, ear stick or venipuncture, complete the following:

☐ **From healthy, non pregnant, adult subjects who weigh at least 110 pounds**. For a minimal risk application, the amount of blood drawn from these subjects may not exceed 550ml in an 8 week period and collection may not occur more frequently than 2 times per week.

Volume per blood draw: _____ml

Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.)

_____

X **From other adults and children considering age, weight, and health of subject.** For a minimal risk application, the amount of blood drawn from these subjects may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period, and collection may not occur more frequently than 2 times per week.

Volume per blood draw: ___3__ml

Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.)___7

Review of Chart, Images, Specimens

Provide the date range for collection of data and/or specimens that will be included in your research dataset. *Example: 01/01/2000 to 12/31/2013* or all records through dd/mon/yyyy.

Date range:

Check all that apply:

☐ This study involves only data and/or specimens that exist at the time this application is submitted to the IRB (IRB submission date). No data or specimens will be collected beyond this date.

X This study involves only data and/or specimens that will be collected after submission to the IRB.

☐ The study involves data and/or specimens that exist at the time of submission to the IRB **and** data and/or specimens that will be collected after submission to the IRB, for example a study that includes collection of existing data and prospective collection of specimens.

☐ Data and/or specimens used in this study are collected under another IRB protocol. *When checked, provide the IRB number(s) from which the research material will be obtained. When appropriate, check the box below to attest that subjects have provided consent for future use of their data and/or specimens, as described in this protocol*.

IRB Number/s - Data Only: _____

IRB Number/s - Specimens Only: _____

IRB Number/s - Data and Specimens:_____

□ Subjects have provided consent for use of their data and/or specimens, as described in this protocol.

☐ Other data sources will be utilized in this study, e.g. receiving data/specimens from an external party. When checked, provide all data sources: