Safety, efficacy, and cost-effectiveness of a reduced Infliximab infusion protocol

Principal Investigator: Chien-Huan Chen, M.D., PhD.
Division of Gastroenterology
Washington University in St Louis School of Medicine
660 South Euclid Ave
St Louis MO 63110

Coordinating Center: Washington University School of Medicine

Co-Investigators: Suha Abushamma, M.D.

Study Coordinator: Suha Abushamma, M.D.
Statistician: To be determined

Protocol Version: 1
Amendment: 3
Protocol Date: May 5, 2022

Safety, efficacy, and cost-effectiveness of a reduced Infliximab infusion protocol

Principal Investigator Signature Page

Principal Investigator (printed):

Name of Institution:

PI Signature *Date*

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/HRPO procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.

TABLE OF CONTENTS

1 Background and Rationale

1.1 Infliximab use in IBD

Inflammatory bowel disease (IBD) affects 349 per 100,000 adults in the United States and is associated with significant morbidity and mortality [1-2]. Infliximab is an effective and commonly used medication to treat patients with IBD, but a main safety concern is an antibody-induced infusion reaction [3]. The incidence of infusion reactions is ~6.5%, with mild, moderate, or severe reactions occurring in 3.1%, 1.2%, and 1% of infusions, respectively [4]. Because of the concern for infusions reactions, infliximab is FDA approved to be infused over 2 hours or more. The typical interval for infusions is every eight weeks but is at times reduced to every 4 weeks in patients with IBD. This infusion time represents a significant inconvenience to patients who receive regular maintenance infusions [3].

1.2 Accelerated Infliximab Infusions

Multiple studies outside of the United States have demonstrated that a shortened infusion time to one hour, and even thirty minutes is safe and tolerable with similar rates of infusion reactions compared to an infusion time of two hours [5-13]. However, these studies have differed in dosing, interval, pre-medication allowed in the study, and they are not randomized controlled studies. It has also been shown that reducing infusion times leads to cost savings and increased patient satisfaction [14]. A recent study conducted in the United States at the University of California in San Francisco, confirmed that a shortened infusion time of one hour is safe and tolerated [15].

1.3 Rationale

Our hypothesis is that a shortened infusion time to one hour will be safe and tolerated, with equal infusion reaction rates compared to two-hour infusion.

2 Objectives

2.1 Primary Objective

To compare the **safety and tolerability** (infusion reaction rate) of an infliximab infusion time of one hour versus the standard two-hour infusion.

2.2 Secondary Objectives

1. Cost savings analysis of shortened infliximab infusion time
2. Assess effect of concomitant immunomodulators and premedications on rate of infusion reactions

3 Eligibility Criteria

3.1 Inclusion Criteria

1. Must be at least 18 years of age
2. Must have a diagnosis of IBD
3. Must be receiving Infliximab or biosimilar drug infusions for IBD at one of our infusion centers – Center for Advanced Medicine, Barnes-Jewish West County, or Barnes-Jewish South County infusion centers, or BJC home pharmacy
4. Must tolerate the three induction doses or be tolerating current maintenance dosing without an infusion reaction to qualify for randomization.

3.2 Exclusion Criteria

1. Those receiving Infliximab for an indication other than IBD (we will include patients receiving infliximab or biosimilar drug for both IBD and an additional autoimmune disease)
2. Patients with history of a moderate or severe infusion reactions to infliximab or to an infliximab biosimilar as defined in section 7
3. Patients with known antidrug antibodies to infliximab
4. Patients who are restarting infliximab (patients who have received infliximab within the past year but have now had an interval greater than 13 weeks between prior dose) must tolerate the three induction doses to qualify for randomization
5. Patients receiving an additional infusion concomitant with infliximab (e.g. IV iron)
6. Patients who decline to participate in the trial

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4 REGISTRATION PROCEDURES

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below through review of the electronic medical record (EMR).

1. Patient name and contact information (telephone number, fax number and email address)
2. Patient's age, race, sex, and DOB
3. Diagnosis of IBD
4. Infliximab infusion history
5. Assessment for exclusion criteria listed in 3.2

4.2 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. Patients will also be identified by first, middle, and last initials. If the patient has no middle initial, a dash will be used.

4.3 Patient assignment

Consenting and eligible participants will be randomly assigned to one of two arms using a research randomization tool. There will be one control arm and one intervention arm. Participants in the first arm will undergo a traditional infusion time of two hours. The second arm will be patients who undergo an infusion time of one hour. Infusion reaction will be recorded. Patients from the intervention groups who have a moderate or severe infusion reaction, as defined in section 7, will be removed from the intervention groups back to 2-h infusions. Their subsequent infusions will not be included in the final analysis of 2-h infusions.

5 Study Procedures

5.1 Recruitment

Adult patients with IBD who are receiving or are scheduled to start infliximab infusions will be screened for inclusion in the study. Patients will be identified from the gastroenterology clinic as well as outpatient infusion centers in the Center for Advanced Medicine, Barnes-Jewish West County, or Barnes-Jewish South County locations. Those subjects who qualify for the study based on inclusion/ exclusion criteria will be invited to participate. Once eligibility is confirmed, the patient will be contacted by phone, or in person in the clinic or infusion center, by one of the members of the research team. They will discuss the purpose of the study, the three arms, risks, and benefits of the study using an approved phone script. The patient will then be invited to participate. The consent process will take place over the phone when the patient is contacted or in person when they present for an infusion. Those patients who wish to participate will provide verbal consent. They will then proceed with the scheduled infusions. Patient allocation will take place after the patient is consented and before the day of the infusion.

5.2 Intervention

After consent is obtained the patients will be assessed for appropriateness of a shortened infusion time. Patient that have tolerated their three induction doses without an infusion reaction, as well as patients who are already on maintenance dosing and do not have a history of an infusion reaction, will be randomized to either receive a one hour infusion of infliximab, or to stay on the standard 2-h infusion. Infusion reactions will be recorded for each group as outlined in section 7. Additional information including IBD type, demographic information, pre-medication use, and concomitant immunomodulator therapy will be recorded as well. All infusion doses as well as infusion intervals will be eligible for inclusion in the study. Drug dosing and intervals will be determined by the prescribing physician and left to their discretion.

Patients in the intervention group who develop a moderate or severe infusion reaction as defined in section 7 will be removed from the intervention group and placed back on 2-h infusions. These future infusions will not be included in the study. Patients with a mild infusion reaction will continue in their assigned group (intervention or control).

6 REGULATORY AND REPORTING REQUIREMENTS

Rates of infusion reactions will be continuously recorded and reported to an oversight committee to allow for safety monitoring.

7 Data and Safety Monitoring Plan

Acute infusion reactions will be defined as any reaction occurring during or within 1 hour after completion of the infusion. They will be separated into mild reactions and moderate/severe reactions as outlined below.

1. Mild/Localized Reaction
    a. Pruritus
    b. Flushing (facial erythema)
    c. Rash/Urticaria
    d. Rigors
    e. Swelling
2. Moderate/Severe Reaction
    a. Fever (temperature > 38.3 degree Celsius)
    b. Heart Rate greater than 120
    c. Dyspnea/Shortness of breath
    d. Decrease in consciousness
    e. Hypotension defined as decrease in baseline SBP by >20 mmHg or SBP <85
    f. Bronchospasm or laryngospasm
    g. Anaphylactic shock

The treatment plan for infusion reactions will be as follows:

1. Mild/Localized Reaction
    a. Pruritus, flushing, rash, or swelling
        i. Stop infusion
        ii. Administer diphenhydramine 25mg IV x 1
        iii. Administer famotidine 20mg IV x 1
        iv. Repeat steps ii, and iii x 1 PRN if no symptom improvement after 15 min.
        v. Notify MD
        vi. Vital signs every 15 minutes until symptoms resolve
        vii. After symptom resolution, restart infusion at 50% of previous rate
    b. Rigors
        i. Stop infusion
        ii. Administer meperidine 25mg IV x 1 only (not to be given if greater than 2 hours post infusion cessation)
        iii. Notify MD
        iv. Vital signs every 15 minutes until symptoms resolve
        v. After symptom resolution, restart the infusion at 50% of previous rate
2. Moderate to Severe Reactions
    a. Stop infusion
    b. Administer diphenhydramine 50mg IV x 1
    c. Administer methylprednisolone 125mg IV x 1
    d. Administer famotidine 20mg IV x 1
    e. Repeat steps b, c, and d x 1 PRN if symptoms do not resolve within 15 min.
    f. If hypotension occurs (decrease in baseline SBP by >20 mmHg or SBP <85mmHg
        i. Administer epinephrine (1:1000) 0.3mg IM x 1. Repeat x 1 PRN if hypotension does not resolve within 15 min.
    g. Administer normal saline IV, wide open
    h. Place nasal cannula oxygen at 2L/minute
    i. Notify MD

j. Check vital signs every 5 minutes until stable, then every 15 minutes until symptoms resolve
k. The time and rate of infusion restart to be determined by MD

8 Statistical Considerations

8.1 Sample Size Calculations

Our sample size calculation was based on an infusion reaction rate of 3%, as suggested by recent studies. In order to show a non-inferiority of the accelerated infusion time assuming an infusion reaction rate of 3% while allowing for a 12% non-inferiority limit, a total of 90 patients (45 in each group) would be needed. This would provide a power of 80% and significant alpha of 0.05.

8.2 Analysis methods

This study will collect both categorical and quantitative demographic variables, infusion details, and infusion reaction details. Premedication details and comcomitant immonomodulator therapy will also be recorded. All information will be transferred into an encrypted database. The categorical variables will be summarized using frequencies and percents, while the quantitative variables will be summarized using means and standard deviations. Chi square test will be used for categorical variables while student's t test will be used for quantitative variables to test the difference between the study groups. Additionally, multivariable analysis will be used in order to identify factors associated with an increased risk of infusion reaction. The statistical software program SPSS will be used for analysis. A two-sided p value of < 0.05 will be considered significant.

9 References

1. Kappelman MD, Rifas-Shiman SL, Kleinman K, et al The prevalence and geographic distribution of Crohn's disease and ulcerative colitis in the United States. Clin Gastroenterol Hepatol. 2007;5:1424-9.
2. Langholz E. Current trends in inflammatory bowel disease: the natural history. Ther Adv Gastroenterol. 2010;3:77-86
3. REMICADE (infliximab) [package insert]. Janssen Biotech, Inc: Horsham, PA. Revised on June 2018.
4. Cheifetz A, Smedley M, Martin S, et al The incidence and management of infusion reactions to infliximab: a large center experience. Am J Gastroenterol. 2003;98:1315-24.
5. Breynaert C, Ferrante M, Fidder H, et al Tolerability of shortened infliximab infusion times in patients with inflammatory bowel diseases: a single-center cohort study. Am J Gastroenterol. 2011;106:778-85.
6. Clare DF, Alexander FC, Mike S, et al Accelerated infliximab infusions are safe and well tolerated in patients with inflammatory bowel disease. Eur J Gastroenterol Hepatol. 2009;21:71-5.
7. Lee TW, Singh R, Fedorak RN. A one-hour infusion of infliximab during maintenance therapy is safe and well tolerated: a prospective cohort study. Aliment Pharmacol Ther. 2011;34:181-7.
8. McConnell J, Parvulescu-Codrea S, Behm B, et al Accelerated infliximab infusions for inflammatory bowel disease improve effectiveness. World J Gastrointest Pharmacol Ther. 2012;3:74-82.
9. Belhassan M, Zeitoun JD, Lefevre JH, et al Infliximab infusion time in patients with inflammatory bowel diseases: is longer really safer? Clin Res Hepatol Gastroenterol. 2013;37:189-92.
10. Neef HC, Riebschleger MP, Adler J. Meta-analysis: rapid infliximab infusions are safe. Aliment Pharmacol Ther. 2013;38:365-76.
11. Babouri A, Roblin X, Filippi J, et al Tolerability of one hour 10 mg/kg infliximab infusions in inflammatory bowel diseases: a prospective multicenter cohort study. J Crohns Colitis. 2014;8:161-5.

12. Van Assche G, Vermeire S, Noman M, et al Infliximab administered with shortened infusion times in a specialized IBD infusion unit: a prospective cohort study. J Crohns Colitis. 2010;4:329-33.
13, Rozette NA, Hellauer CM, McKee C, et al Evaluation of Rapid vs Standard Infliximab Infusions in the Pediatric Population. Inflamm Bowel Dis. 2018;24(9):2007-2014.
14. Mazzuoli S, Tricarico D, Demma F, et al Accelerated infliximab infusion: safety, factors predicting adverse events, patients' satisfaction and cost analysis. A cohort study in IBD patients. PLoS ONE. 2016;11:e0166443.
15. Ma D, Wong W, et. Al. Safety and Tolerability of Accelerated Infliximab Infusions in Patients with Inflammatory Bowel DIsease. Am J Gastroenterol. 2019;114(2):352-354.