Principal Investigator

First Name: Raymond
Last Name: Cross
Degree: MD, MS
Primary Affiliation: University of Maryland, Baltimore
E-mail: rcross@medicine.umaryland.edu
Phone number: 4107063387
Address: 100 North Greene Street
LL
City: Baltimore
State or Province: MD
Zip or Postal Code: 21201
Country: United States
SCOPUS ID: 7202235843

2014-0334

General Information

Key Personnel (in addition to PI): **First Name:** Guruprasad
Last name: Jambaulikar
Degree: MBBS, MS
Primary Affiliation: University of Maryland, Baltimore

First Name: Sandra
Last name: Quezada
Primary Affiliation: UMB

First Name: Dhyan
Last name: Rajan
Degree: MD
Primary Affiliation: University of Maryland Medical Center, Baltimore

First Name: Erik
Last name: Barr
Degree: MD
Primary Affiliation: University of Maryland, Baltimore

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.

cross_jambaulikar_yoda-coi_oct2014.pdf
quezada_yoda.pdf
coi_-_dr.pdf
coi_-_eb.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

Associated Trial(s): NCT00036439 - A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients With Active Ulcerative Colitis
NCT00094458 - Multicenter, Randomized, Double-Blind, Active Controlled Trial Comparing REMICADE® (infliximab) and REMICADE plus Azathioprine to Azathioprine in the Treatment of Patients with Crohn's Disease Naive to both Immunomodulators and Biologic
NCT00207662 - ACCENT I - A Randomized, Double-blind, Placebo-controlled Trial of Anti-TNFa Chimeric Monoclonal Antibody (Infliximab, Remicade) in the Long-term Treatment of Patients With Moderately to Severely Active Crohn's Disease
NCT00207766 - ACCENT II - A Randomized, Double-blind, Placebo-controlled Trial of Anti-TNF Chimeric Monoclonal Antibody (Infliximab, Remicade) in the Long Term Treatment of Patients With Fistulizing CROHN'S Disease
What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Gender Differences in Weight Gain in Patients with Inflammatory Bowel Disease Treated with Infliximab

Narrative Summary:
Women frequently ask if anti-TNFs result in weight gain; high drug levels may cause weight gain. We will compare weight in patients and determine if drug levels are linked to weight gain. If differences are present, future studies to optimize drug levels to avoid excess weight gain will be planned.

Scientific Abstract:
a. Background: In clinical practice, women frequently complain of excess weight gain after initiating and maintaining treatment with an anti-TNF agent. At present, there are no studies in patients with inflammatory bowel disease (IBD) addressing weight gain after treatment with an anti-TNF.
b. Objectives: To determine the difference in weight from baseline to end of follow up and to identify factors associated with "excess" weight gain in IBD patients induced and maintained on infliximab (IFX).
c. Study Design: Retrospective cohort study.
d. Participants: Participants with moderate to severe CD and UC that received IFX induction and maintenance therapy as part of pivotal clinical trials of IFX for IBD.
e. Main Outcome Measures:
1) Difference in absolute and percent change in weight in women and men
2) Association between IFX trough levels and the change in weight from baseline
3) Association between gender and change in weight adjusting for potential confounding factors
f. Statistical Analysis: The within group difference in absolute and relative weight change will be compared in the sub-group of men and women using the paired t test. Differences in change in weight between men and women from baseline to last follow up will be compared using the t test. Correlation analyses will determine the association between trough IFX level and the relative increase in weight. The association between demographic and clinical factors and increase in weight will be measured using multivariate logistic and linear regression model.

Brief Project Background and Statement of Project Significance:
Anti-TNFs are effective at both induction and maintenance of remission for patients with luminal and fistulizing CD and UC1-12. Providers are still trying to understand how to optimize anti-TNFs as 20-40% of patients will not respond to therapy initially (primary non-response)1,4 and 40% of patients lose response over time13. Vande

Casteele demonstrated that a trough IFX less than 2.2 mcg/ml at week 14 after IFX induction for UC is associated with IFX discontinuation (LR 3.1, p=0.0026)14. Afif demonstrated that increasing the dose of IFX is effective at recapturing response if trough levels are undetectable whereas optimizing IFX dosing in patients with antibodies to IFX was less effective than changing anti-TNF agents15. Detectable IFX trough levels are associated with improved clinical outcomes in patients with IBD16. Several clinical factors influence anti-TNF levels. Anti-drug antibodies (ADA) increase clearance and decrease anti-TNF levels5,17,18. Concurrent use of an immune suppressant decrease ADA and increase anti-TNF levels17,19-21. High baseline TNF levels22,23, high CRP, and low serum albumin all increase drug clearance and decrease anti-TNF levels24-26. Heavier patients and men clear anti-TNFs more rapidly and have lower anti-TNF levels24,27,28.

Our interest in evaluating differences in weight after initiating anti-TNF started at the “bedside”. Frequently, women report excess weight gain after initiating an anti-TNF. Weight gain has been attributed to control of inflammation after anti-TNF initiation followed by return of appetite and weight gain. However, a February 60 Minutes report “Sex Matters” triggered awareness in the medical community regarding potential gender differences in drug metabolism resulting in a new policy requiring sex and gender inclusion plans in preclinical research29. Weight gain after anti-TNF therapy has been reported in psoriasis, ankylosing spondylitis (AS), psoriatic arthritis (PSA), and rheumatoid arthritis (RA). A retrospective study of 150 patients with RA, AS, and PSA noted weight gain in 13% of patients with an mean of 5.5 kg30. Similarly, mean weight gain of 4.8+/-5 kg was observed in 16 patients with psoriasis treated with IFX for 3 years31. Only one study has examined factors associated with weight gain in patients treated with anti-TNF; lower baseline BMI but not gender was associated with weight gain32. No studies in the IBD population have examined weight gain after anti-TNF therapy and none have studied the association between anti-TNF levels and weight gain.

We hypothesize that women treated with anti-TNF agents achieve higher anti-TNF resulting in a greater increase in weight compared to men.

If we determine that women do not experience a higher relative increase in weight after initiation of anti-TNF then men, this information will be important for providers to reassure women about weight gain after starting anti-TNF agents. If gender-specific changes in weight are observed and if these changes correlate with anti-TNF levels, further prospective studies can be planned to determine if reducing the dose of anti-TNF to achieve a lower trough level can reduce weight gain.

Specific Aims of the Project:
We propose use of data from A Crohn’s Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen (ACCENT I), A Crohn’s Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen in Patients with Fistulizing Crohn’s Disease (ACCENT II), The Study of Biologic and Immunomodulator Naïve Patients in Crohn’s Disease (SONIC), and the Active Ulcerative Colitis Trial (ACT 1) to address the following specific aims.

1. Determine the absolute difference in body weight from baseline to end of follow up in men and women induced and maintained on IFX.
2. Determine the relative difference in body weight from baseline to the end of follow up in men and women induced and maintained on IFX.
3. Determine the association between the relative increase in weight and trough IFX levels in patients induced and maintained on IFX.
4. Determine the demographic and clinical factors associated with excess weight gain defined as the upper quartile of relative gain in weight from baseline to end of follow up in patients induced and maintained on IFX.

What is the purpose of the analysis being proposed? Please select all that apply. New research question to examine treatment safety

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:
Patients with moderate to severe CD and UC treated with IFX and placebo for both induction and maintenance of remission as part of the ACCENT I, ACCENT II, SONIC, and ACT I trial will be included for analysis (see Table 1). Only participants that completed the entire one year of follow up will be included for analysis.

Table 3: Number of Participants from Pivotal IFX Clinical Trials to be Included in Proposed Study (IFX treated patients only)
Trial Number of Participants
ACCENT I 225
ACCENT II 96
SONIC 85
ACT 1 146
Total=552
Baseline demographic and clinical variables will be collected from all participants. Body weight at each research visit will be collected; however the primary comparison will be the difference in body weight from baseline (week 0) to end of study (week 54 for ACCENT I, ACCENT II, and ACT 1 and week 50 for SONIC).

Statistical Analysis Plan:
The within group difference in absolute weight change will be compared in the sub-group of men and women using the paired t test. Differences in change in weight between men and women from baseline to last follow up will be compared using the t test. If the results are not normally distributed, the Wilcoxon signed rank test will be used. The relative change in weight from baseline will be obtained by calculating the increase in body weight from baseline to last follow up. For example, a 70 kg woman experienced a 5 kg increase in body weight from the baseline to the last follow up visit. Hence, she experienced a 7.1% increase in body weight. Use of relative changes in body weight will be helpful to account for baseline differences in body weight between men and women. Differences within sub-groups will be compared using the paired t test whereas differences between sub-groups will be compared using the t test. We will then categorize the change in weight from baseline into quartiles. IFX levels at week 14 and 54, if available, will be compared among the quartiles of patients with different levels of weight gain using ANOVA. In review of the methods from ACCENT I, ACCENT II, and Act 1, it is implied that IFX levels were measured; however they were not reported. If IFX levels are not available, thPower Calculations: ACCENT I, ACCENT II, SONIC, and ACT 1 were comprised of approximately 50% women. Only ACT 1 reports a standard deviation for body weight (at baseline). The mean standard deviation across the three treatment arms in ACT 1 was 17.0. Assuming a type 1 error rate of 5% and a type 2 error rate of 20%, we will be able to detect a 4.1 kg increase or decrease in weight.

Project Timeline:
Once approved, we anticipate that it will take approximately one year to complete the project. After notification of approval, we will seek expedited approval from the Human Subjects Research Office at the University of Maryland, Baltimore. On average, expedited approval takes 5 weeks to obtain. The PI (Raymond Cross, MD, MS) and research staff (Guruprasad Jambaulikar, MBBS, MPH) will schedule a meeting with a senior biostatistician (Patrician Langenberg, PhD) to review the data and the statistical analysis plan. At that time, either the PI and research staff or Dr. Langenberg will develop a data dictionary, write code, and construct regression models to analyze the data. We estimate the initial data preparation and analysis will take up to 60 days. The preliminary results will be reviewed by the PI and research staff. If needed, additional analyses will be performed. We anticipate submitting the results to an annual gastroenterology meeting (Digestive Diseases Week, American College of Gastroenterology Annual Meeting, or Advances in IBD) for presentation. We will then begin drafting the manuscript. Publication of the results will be dependent on the peer review process but could take up to 6 months.

Dissemination Plan:
The target audience for our findings will be gastroenterologists, allied health professionals, nurses, and surgeons with an interest in the care of patients with IBD. We first plan to disseminate the results in abstract form as an oral or poster presentation at an annual gastroenterology meeting (Digestive Diseases Week, American College of Gastroenterology Annual Meeting, or Advances in IBD). We anticipate that our findings, positive or negative, will be enthusiastically received. We than plan on drafting a manuscript to be submitted to Gastroenterology, American Journal of Gastroenterology, Clinical Gastroenterology and Hepatology, or Inflammatory Bowel Diseases.

Bibliography:
1. Targan SR, Hanauer SB, van Deventer SJ, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. N Engl J Med. Oct 9 1997;337(15):1029-1035.
2. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med. May 6 1999;340(18):1398-1405.
3. Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. N Engl J Med. Feb 26 2004;350(9):876-885.

4. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet. May 4 2002;359(9317):1541-1549.
5. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. Apr 15 2010;362(15):1383-1395.
6. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. Dec 8 2005;353(23):2462-2476.
7. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology. Jan 2007;132(1):52-65.
8. Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology. Feb 2006;130(2):323-333; quiz 591.
9. Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. Feb 2012;142(2):257-265 e251-253.
10. Sandborn WJ, Schreiber S, Feagan BG, et al. Certolizumab pegol for active Crohn's disease: a placebo-controlled, randomized trial. Clin Gastroenterol Hepatol. Aug 2011;9(8):670-678 e673.
11. Schreiber S, Khaliq-Kareemi M, Lawrance IC, et al. Maintenance therapy with certolizumab pegol for Crohn's disease. N Engl J Med. Jul 19 2007;357(3):239-250.
12. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous Golimumab Maintains Clinical Response in Patients with Moderate-To-Severe Ulcerative Colitis. Gastroenterology. Jun 13 2013.
13. Gisbert JP, Panes J. Loss of response and requirement of infliximab dose intensification in Crohn's disease: a review. Am J Gastroenterol. Mar 2009;104(3):760-767.
14. Vande Casteele N, Gils A, Singh S, et al. Antibody response to infliximab and its impact on pharmacokinetics can be transient. Am J Gastroenterol. Jun 2013;108(6):962-971.
15. Afif W, Loftus EV, Jr., Faubion WA, et al. Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. Am J Gastroenterol. May 2010;105(5):1133-1139.
16. Maser EA, Villela R, Silverberg MS, Greenberg GR. Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease. Clin Gastroenterol Hepatol. Oct 2006;4(10):1248-1254.
17. Baert F, Noman M, Vermeire S, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. N Engl J Med. Feb 13 2003;348(7):601-608.
18. Karmiris K, Paintaud G, Noman M, et al. Influence of trough serum levels and immunogenicity on long-term outcome of adalimumab therapy in Crohn's disease. Gastroenterology. Nov 2009;137(5):1628-1640.
19. Vermeire S, Noman M, Van Assche G, Baert F, D'Haens G, Rutgeerts P. Effectiveness of concomitant immunosuppressive therapy in suppressing the formation of antibodies to infliximab in Crohn's disease. Gut. Sep 2007;56(9):1226-1231.
20. Hanauer SB, Wagner CL, Bala M, et al. Incidence and importance of antibody responses to infliximab after maintenance or episodic treatment in Crohn's disease. Clin Gastroenterol Hepatol. Jul 2004;2(7):542-553.
21. Lichtenstein GR, Diamond RH, Wagner CL, et al. Clinical trial: benefits and risks of immunomodulators and maintenance infliximab for IBD-subgroup analyses across four randomized trials. Aliment Pharmacol Ther. Aug 2009;30(3):210-226.
22. Ainsworth MA, Bendtzen K, Brynskov J. Tumor necrosis factor-alpha binding capacity and anti-infliximab antibodies measured by fluid-phase radioimmunoassays as predictors of clinical efficacy of infliximab in Crohn's disease. Am J Gastroenterol. Apr 2008;103(4):944-948.
23. Olsen T, Goll R, Cui G, Christiansen I, Florholmen J. TNF-alpha gene expression in colorectal mucosa as a predictor of remission after induction therapy with infliximab in ulcerative colitis. Cytokine. May 2009;46(2):222-227.
24. Fasanmade AA, Adedokun OJ, Ford J, et al. Population pharmacokinetic analysis of infliximab in patients with ulcerative colitis. Eur J Clin Pharmacol. Dec 2009;65(12):1211-1228.
25. Fasanmade AA, Adedokun OJ, Blank M, Zhou H, Davis HM. Pharmacokinetic properties of infliximab in children and adults with Crohn's disease: a retrospective analysis of data from 2 phase III clinical trials. Clin Ther. Jul 2011;33(7):946-964.
26. Wolbink GJ, Voskuyl AE, Lems WF, et al. Relationship between serum trough infliximab levels, pretreatment C reactive protein levels, and clinical response to infliximab treatment in patients with rheumatoid arthritis. Ann Rheum Dis. May 2005;64(5):704-707.
27. Ternant D, Aubourg A, Magdelaine-Beuzelin C, et al. Infliximab pharmacokinetics in inflammatory bowel disease patients. Ther Drug Monit. Aug 2008;30(4):523-529.
28. Klaasen R, Wijbrandts CA, Gerlag DM, Tak PP. Body mass index and clinical response to infliximab in rheumatoid arthritis. Arthritis Rheum. Feb 2011;63(2):359-364.
29. Clayton JA, Collins FS. Policy: NIH to balance sex in cell and animal studies. Nature. May 15 2014;509(7500):282-283.

30. Lutf A, Hammoudeh M. Weight Gain and Hair Loss during Anti-TNF Therapy. International journal of rheumatology. 2012;2012:593039.
31. Florin V, Cottencin AC, Delaporte E, Staumont-Salle D. Body weight increment in patients treated with infliximab for plaque psoriasis. J Eur Acad Dermatol Venereol. Feb 2013;27(2):e186-190.
32. Brown RA, Spina D, Butt S, Summers GD. Long-term effects of anti-tumour necrosis factor therapy on weight in patients with rheumatoid arthritis. Clin Rheumatol. Mar 2012;31(3):455-461.