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General Information

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

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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): 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
What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Impact of infliximab concentrations on combination therapy for Crohn's disease

Narrative Summary:
Infliximab is a medication used for treatment of Crohn's disease. One landmark randomized controlled trial of infliximab monotherapy compared to infliximab in combination with another medication (azathioprine) demonstrated superiority of the combined regimen. However, patients in the combination therapy arm had higher infliximab trough concentrations raising the possibility that the benefit was actually from higher infliximab drug levels. We propose to perform a post-hoc analysis of the study data to determine the optimal infliximab concentration, and to assess if infliximab concentration is associated with clinical remission regardless of combination therapy.

Scientific Abstract:
Background: Combination therapy with infliximab and an immunomodulator is now thought to be the most effective treatment for Crohn's disease. However the role of combination therapy may be due to increase the trough concentration of infliximab. It is unknown if dose optimized infliximab would be inferior or equivalent to combination therapy.
Objectives: To determine if infliximab trough concentration is an independent predictor of clinical remission in a cohort of patients with Crohn's disease.
Study Design: This is a post hoc analysis of a prospective blinded randomized controlled trial of infliximab monotherapy compared to infliximab in combination with an immunomodulator.
Participants: Patients enrolled in the SONIC trial (NCT00094458) in the infliximab monotherapy arm and infliximab in combination with immunomodulator arm.
Main outcome measure: Clinical remission is the main outcome measure and infliximab concentration is our exposure (predictor) of interest.
Statistical Analysis: Logistic regression will be used to determine if infliximab concentration is an independent predictor of clinical remission. Additionally ROC curves will be used to determine the optimal infliximab concentration for both monotherapy and combination therapy.

Brief Project Background and Statement of Project Significance:
Infliximab was approved for the treatment of Crohn's disease in 1998 and the optimal way to dose is the medication is still not clear. Initially infliximab was dosed episodically, however scheduled therapy proved to be superior to intermittent therapy.(Rutgeerts, Feagan et al. 2004) Following that it was unclear if infliximab should be given alone or in combination with an immunomodulator. Early trials did not seem to identify a benefit of two drugs, and given the concern for increased cost and adverse events, infliximab was often used as monotherapy.(Hanauer, Feagan et al. 2002) However a randomized controlled trial (SONIC) demonstrated that combination therapy was superior to infliximab monotherapy for clinical remission.(Colombel, Sandborn et al. 2010) In the SONIC trial, the authors noted that the infliximab concentration was higher in the combination therapy group, however this was not further assessed. Most recently, therapeutic drug monitoring with titration of infliximab to a goal trough has been proposed as the optimal way for dosing. (Vaughn, Martinez-Vazquez et al. 2014, Vande Casteele, Ferrante et al. 2015, Vaughn, Sandborn et al. 9000) This has led to the concept of optimized monotherapy as an alternative to combination therapy.(Vaughn, Martinez-Vazquez et al. 2014)

The question at hand is what is the benefit of combination therapy? Multiple reports, including the SONIC data, demonstrate that combination therapy is associated with a higher infliximab trough levels. Our central hypothesis is that the benefit of combination therapy is in increasing the infliximab concentration. A post hoc analysis of the SONIC trial will provide the basis to support further prospective clinical trials to assess optimized monotherapy. Additionally, this study will have an immediately impact on clinical practice by identifying optimal infliximab concentrations for monotherapy as well as combination therapy, which are likely to be different. Currently many authors suggest a trough cut off of higher than 3ug/mL.(Cornillie, Hanauer et al. 2014) However it is unknown if the optimal cut off is different if on infliximab monotherapy or combination therapy. The SONIC data is uniquely poised

to answer that question. This study will continue to inform physicians on the optimal dosing for infliximab as well as advance our knowledge of the role of therapeutic drug monitoring in Inflammatory Bowel Disease.

Specific Aims of the Project:
SA 1: To assess if infliximab trough concentration is independently associated with clinical remission. Through a post hoc analysis we will build a logistic regression model to determine if infliximab concentration can independently predict clinical remission at 26 weeks. We hypothesize that infliximab concentration is associated with clinical remission independently of combination therapy use. We will also explore if infliximab concentration can predict clinical remission at 1 year.

SA 2: Determine the optimal trough concentration for infliximab monotherapy and combination therapy. We will develop receiver operating characteristic (ROC) curves of infliximab trough concentration and CRP to determine the ideal post induction (week 14) infliximab trough concentration between each group (monotherapy and combination therapy). We hypothesize that a higher infliximab concentration is needed in the monotherapy group compared to the combination therapy group.

What is the purpose of the analysis being proposed? Please select all that apply. New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations
Research that confirms or validates previously conducted research on treatment effectiveness

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:
All patients enrolled in the SONIC trial in either the combination (infliximab plus immunomodulator) or infliximab monotherapy arm will be assessed. Subjects with incomplete data regarding infliximab concentration at week 14 will also be excluded. Subjects who only received an immunomodulator will be excluded.

Main Outcome Measure and how it will be categorized/defined for your study:
Main outcome measure will remain as defined in the study as: steroid free clinical remission at week 26. Clinical remission is defined as CDAI (Crohn's Disease Activity Index) of < 150 points. Clinical remission will be a binary outcome in order to perform logistic regression.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
The main exposure of interest is infliximab concentration. Prior data from ACCENT 1 suggests that week 14 infliximab level can predict clinical remission among all patients.(Cornillie, Hanauer et al. 2014) Thus we will use the post-induction (i.e. week 14) infliximab concentration as our exposure of interest.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:
Co-variates will include: age, sex, race (white), body weight, disease duration, CRP, disease distribution (ileum alone/colon alone/ileocolonic), steroid use (Yes), and azathioprine use (Yes). All first order interactions will be tested for. If certain variables are found to be highly collinear with infliximab trough at week 14, they will be removed from the model. CDAI will not be used in the model to determine sustained response.

Statistical Analysis Plan:
For the primary aim we will build a multivariate logistic regression model to assess if week 14 infliximab concentration is independently associated with clinical remission based on the above co-variates. Descriptive characteristics will be reported as mean (sd) or median (IQR) based on the normality of the data. Infliximab concentrations for responders and non-responders will analyzed in the regression model as a continuous variable. For the purposes of presenting the data infliximab will be broken down be median (IQR) and monotherapy or combination therapy. Box and whiskers plot will be used to visually display infliximab concentration over time.

For our secondary aim we plan to develop receiver operating characteristic (ROC) curves to assess the sensitivity and specificity analysis of week 14 infliximab levels and CRP. We will use known responders and non-responders to assess for determine the optimal cutoff values for CRP decrease and week 14 infliximab concentration. This analysis will be performed for the entire cohort, then subdivided among infliximab monotherapy and infliximab combination therapy.

Project Timeline:
Once approved we anticipate 4 months for data collection and review. Following this we anticipate 4 months for statistical analysis to generate the tables and figures consistent with logistic regression analysis and ROC curves. Another 2-3 months will then be used to write and submit a manuscript.

Dissemination Plan:
The target audience for this includes practicing gastroenterologists and inflammatory disease specialists. This topic is particularly germane given the new concept of therapeutic drug monitoring in Inflammatory Bowel Diseases. This issue has received much attention at recent national conferences, including Digestive Diseases Week and the Advances in IBD conference. It is expected that data will be prepared in manuscript form suitable for presentation in journals such as the American Journal of Gastroenterology, Clinical Gastroenterology and Hepatology, or Inflammatory Bowel Diseases.

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