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General Information

Key Personnel (in addition to PI): **First Name:** Konstantinos
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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.
How did you learn about the YODA Project?: Colleague

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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): NCT01190839 - Prospective, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial Comparing REMICADE (Infliximab) and Placebo in the Prevention of Recurrence in Crohn's Disease Patients Undergoing Surgical Resection Who Are at Increased Risk of
What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Serum infliximab concentration and prevention of clinical or endoscopic post-operative recurrence after an ileocolonic resection for Crohn's disease

Narrative Summary:
Crohn's disease (CD) often requires an ileocolonic resection when pharmacological treatment fails. However, 30% of patients will require a second resection within 10 years. This can be prevented by anti-tumor necrosis factor (TNF) therapy. Evaluation of serum drug concentration and anti-drug antibodies can optimize efficacy and cost of anti-TNF therapy. The aim of the study is to investigate the association between drug concentration and positive therapeutic outcomes in CD patients receiving prophylactic infliximab therapy after an ileocolonic resection. This could improve patients' care potentially reducing the substantial social and economic burden to the community.

Scientific Abstract:
Background: Anti-tumor necrosis factor (TNF) therapy is effective for preventing endoscopic or clinical post-operative recurrence (POR) in patients with Crohn's disease (CD) and an ileocolonic resection. Recent exposure-response relationship studies have revealed a positive correlation between high serum anti-TNF drug concentration and positive clinical outcomes.
Objective: To define the therapeutic window for adequate infliximab concentration associated with favorable therapeutic outcomes in CD patients who receive prophylactic infliximab therapy after an ileocolonic resection for prevention of clinical or endoscopic POR.
Study Design: Post-hoc analysis of the PREVENT study.
Participants: Patients (n=147) who started 5 mg/kg of infliximab every 8 weeks after randomization.
Main outcome measure(s): Association between serum infliximab concentration at week 72 and post-operative endoscopic remission at week 76, sustained clinical remission at week 76 and 104 and deep remission at week 76.
Statistical Analysis: Descriptive statistics will be provided with medians and interquartile range for continuous variables and frequency and percentage for categorical variables. A receiver operating characteristic analysis will be performed for infliximab concentrations to trace thresholds associated with outcomes of interest. Infliximab concentrations will be compared between groups with the Mann-Whitney U and Kruskal Wallis test, as appropriate. Univariate and multivariate analyses will be performed to identify variables associated with outcomes of interest.

Brief Project Background and Statement of Project Significance:
Anti-tumor necrosis factor (TNF) therapy is effective for both prevention and treatment of clinical or endoscopic post-operative recurrence (POR) in patients with Crohn's disease (CD) and an ileocolonic resection.[1-4] Recent studies have revealed an exposure-response relationship suggesting a positive correlation between high serum anti-TNF drug concentration and favorable therapeutic outcomes including clinical, biomarker, and endoscopic remission.[5-11] Nevertheless, there are only limited data regarding the role of therapeutic drug monitoring (TDM) of infliximab when administered prophylactically for prevention of clinical and/or endoscopic POR after an ileocolonic resection for CD.[12,13] Moreover, as treatment options in CD patients who fail anti-TNF therapy and undergo an ileocolonic resection remain currently still limited, emphasis has to be given on rational decision-making, such as the TDM-based therapeutic approach. This project, by defining the adequate infliximab concentration for preventing negative therapeutic outcomes in CD patients after an ileocolonic resection, could be an important first step towards the implementation of a proactive TDM in daily clinical practice. This could potentially improve the patients' care and reduce the substantial social and economic burden to the community by preventing future CD-related hospitalizations and surgeries.

Specific Aims of the Project:
Study Objective: To define the therapeutic window for adequate infliximab concentration associated with favorable therapeutic outcomes in CD patients who receive prophylactic infliximab therapy after an ileocolonic resection for prevention of clinical or endoscopic post-operative recurrence.

Specific Aim 1:
To investigate the association between serum infliximab concentration at week 72 and favorable therapeutic outcomes, including post-operative endoscopic response and remission at week 76, post-operative sustained clinical remission at week 76 and 104 and deep remission at week 76.

Specific Aim 2:

To investigate the association between serum infliximab concentration at week 72 and severe post-operative endoscopic recurrence at week 76.

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 Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:
Post-hoc analysis of the PREVENT (Prospective, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial Comparing REMICADE® [infliximab] and Placebo in the Prevention of Recurrence in Crohn's Disease Patients Undergoing Surgical Resection Who Are at an Increased Risk of Recurrence; ClinicalTrials.gov ID NCT01190839) study, a phase 3, multicenter, placebo-controlled, double-blind, randomized study conducted at 104 sites globally between November 2010 and May 2012 regarding only the patients who started 5 mg/kg of infliximab every 8 weeks after randomization (n=147). [1]

Main Outcome Measure and how it will be categorized/defined for your study:
• Post-operative endoscopic response, defined as a Rutgeerts score of equal or lower than R-i1 [14], at week 76.
• Post-operative endoscopic remission, defined as a Rutgeerts score of R-i0, at week 76.
• Post-operative sustained clinical remission, defined as a CD Activity Index (CDAI) score of equal or lower than 150 [15], at week 76 and week 104.
• Deep remission, defined as both endoscopic and clinical remission, at week 76.
• Severe post-operative endoscopic recurrence, defined as a Rutgeerts score of equal or greater than R-i3, at week 76.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
• Serum infliximab concentration and antibodies to infliximab (ATI) at week 72.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:
• Gender.
• Race.
• Age.
• Disease duration.
• Involved gastrointestinal areas.
• Findings at surgery.
• Age at first ileocolonic resection.
• Concomitant Immunosuppressive drugs.
• Prior Immunosuppressive drugs (thiopurines / methotrexate).
• Prior anti-TNF therapy therapy.
• Prior infliximab therapy.
• Prior intra-abdominal surgeries.
• CDAI score.

Statistical Analysis Plan:
Descriptive statistics will be provided with medians and interquartile range (IQR) for continuous variables and frequency and percentage for categorical variables. A receiver operating characteristic (ROC) analysis will be performed for infliximab concentrations to trace thresholds associated with outcomes of interest. Optimal thresholds will be chosen by using the Youden index, which maximizes the sum of the specificity (SP) and sensitivity (SN) of the ROC curve as previously described.[16] SN, SP, positive predictive value, and negative predictive value will be also calculated. Infliximab concentrations at week 72 will be compared between groups with the Mann-Whitney U test. Serum infliximab concentrations will be categorized also into quartiles. Rates of post-operative endoscopic response or remission at week 76, post-operative sustained clinical remission at week 76 and 104, deep remission at week 76 and severe post-operative endoscopic recurrence at week 76 will be compared across infliximab serum concentration quartiles at weeks 72 with the chi-square test (linear-by-linear association). The Kruskal-Wallis and the chi-square test will be used to compare continuous or discrete variables, respectively, across quartile groups. The Mann-Whitney U test and the chi-square test or the Fisher exact test will be used for univariate analysis to

identify quantitative or categorical variables associated with outcomes of interest, respectively. To determine the independent effects of variables associated with outcomes of interest, a multiple binary logistic regression will be then performed including variables with a P value <0.05 from univariate analysis, based on the Backward Wald selection method. The results will be expressed as odds ratio (OR) with 95% confidence intervals, followed by the corresponding P value. Results will be considered statistically significant when P <0.05. All statistical analyses will be performed by using the SPSS 22.0 software (SPSS, Chicago, IL) and GraphPad Prism version 5.03 for Windows (GraphPad Software, San Diego, CA).

Project Timeline:
It is estimated that it will take 2-3 months to review the appropriate data. Statistical analyses will take another 2-3 months, while manuscript preparation will take approximately 2-3 months. Consequently, the whole project will be completed in 6-9 months.

Dissemination Plan:
The results of this study will be disseminated to patients and care-givers through presentations to national and international medical congresses including DDW), Crohn's and Colitis Foundation of America (CCFA), American College of Gastroenterology (ACG), European Crohn's and Colitis Organization (ECCO) and publication of the data in a high impact medical journal such as the American Journal of Gastroenterology, Clinical Gastroenterology and Hepatology, or the Journal of Crohn's and Colitis and distribution to patients' societies.

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