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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.
How did you learn about the YODA Project?: Scientific Publication

Conflict of Interest

http://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_-_singhs.pdf
http://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_-_proudfootj.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):

1. NCT00036439 - A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients With Active Ulcerative Colitis
2. NCT00096655 - A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients With Active Ulcerative Colitis
3. NCT00336492 - A Phase 3, Randomized, Open-label, Parallel-group, Multicenter Trial to Evaluate the

Safety and Efficacy of Infliximab (REMICADE) in Pediatric Subjects With Moderately to Severely Active Ulcerative Colitis

4. NCT00487539 - A Phase 2/3 Multicenter, Randomized, Placebo-controlled, Double blind Study to Evaluate the Safety and Efficacy of Golimumab Induction Therapy, Administered Subcutaneously, in Subjects with Moderately to Severely Active Ulcerative Colitis
5. NCT00488631 - A Phase 3 Multicenter, Randomized, Placebo-controlled, Double-blind Study to Evaluate the Safety and Efficacy of Golimumab Maintenance Therapy, Administered Subcutaneously, in Subjects With Moderately to Severely Active Ulcerative Colitis

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

Research Proposal

Project Title

Continuing or Stopping 5-ASA in Biologic-Treated Patients with Moderate-Severe Ulcerative Colitis: A Post-Hoc Analysis of RCTs

Narrative Summary:

5-aminosalicylates (5-ASA) are the first line therapy for patients with mild-moderate ulcerative colitis. Approximately 10-20% patients will require escalation to immunomodulators, and 5-10% patients will require escalation of therapy to biologics due to moderate-severe disease and failure of 5-ASA. A significant proportion of patients are continued on 5-ASA even after escalating to biologics, though there is very limited evidence any incremental clinical benefit of continuing 5-ASA. This practice may impose significant economic burden. We will evaluate the impact of continued 5-ASA use on clinical outcomes in biologic-treated patients with moderate-severe UC, through analyses of late stage

Scientific Abstract:

Background: Approximately 5-10% patients with UC escalate to biologic therapy for moderate-severe disease after failure of 5-ASA, but a significant proportion of these patients are still continued on 5-ASA without clear clinical rationale.
Objective: To evaluate the impact of continued 5-ASA use (vs. no concomitant 5-ASA use) in biologic-treated patients with moderate-severe UC.
Study Design: Individual participant level pooled analysis of RCTs of infliximab (IFX) and golimumab (GLM) in patients with UC
Participants: Patients enrolled in phase III RCTs of IFX or GLM in moderate-severe UC, receiving active therapy with biologic agents
Main Outcome Measures: Clinical remission/response and endoscopic remission
Statistical Analysis: We will pool data of patients in active agent arms (IFX/GLM separately) to analyze outcomes, stratified by concomitant use of 5-ASA, using logistic regression analysis. Multivariate regression analysis will be performed after adjusting for confounding variables including age, sex, smoking status, baseline disease activity, concomitant corticosteroids, concomitant immunomodulators.

Brief Project Background and Statement of Project Significance:

5-ASA is the mainstay of therapy for patients with mild-moderate UC. In population-based cohort studies, approximately 88-97% patients with UC received 5-ASA within 1 year of diagnosis.1-8 On long-term follow-up, 60-87% patients continued 5-ASA use at 11-15 years after diagnosis, without significant change over time. Approximately 50% patients with UC require corticosteroids for acute flare despite 5-ASA use, and in steroid-dependent patients, treatment is escalated to immunomodulators and/or biologic agents. In contemporary cohorts, immunomodulators are used in 11-20% patients with UC at 1 year, and 17-27% by 7 years. Likewise, approximately 5-10% patients are escalated to biologic agents for refractory disease. In clinical practice, a significant proportion of these patients who have escalated to biologic therapy are still continued on 5-ASA, without

any evidence supporting incremental benefit of continuing 5-ASA. For example, even in clinical trials of moderate-severe UC, 65-80% patients were concomitantly on 5-ASA at start of trial. This imposes significant economic burden, and is inconsistent with principles of value-based care.
The overall objective of this proposal is to understand whether continued use of 5-ASA in patients treated with anti-TNF improves clinical outcomes such as achieving clinical and/or endoscopic remission. Our central hypothesis is that concomitant use of 5-ASA is not associated with any clinical benefit in anti-TNF-treated patients with moderate-severe UC. The long-term goal of our program is to promote value-based care in UC. The significance of this work lies in systematically informing role of concomitant 5-ASA use in patients who have failed 5-ASA and escalated to biologic therapy. The information generated through this study would be invaluable to inform both science and patient care. From a scientific perspective, if we find evidence of additional benefit to continuing 5-ASA in these refractory patients, it will advance understanding of IBD pathophysiology and merit evaluation of potential mechanisms as to why it may be beneficial (for example, impact on pharmacokinetics of biologic therapy, etc.). From a clinical perspective, information generated from this study on treatment response to biologic therapy, will be generalizable and directly applicable to patient care, informing clinical guidelines and offering potential for promoting value-based in patients with IBD.

Specific Aims of the Project:

Specific aim #1: To compare IBD disease activity and outcomes in patients who are concomitantly on 5-ASA vs. stopped 5-ASA, in post-hoc analysis of phase III RCTs of IFX and GLM in UC.
Hypothesis: As compared to stopping 5-ASA, concomitant use of 5-ASA will not be associated with improvement in rates of achieving clinical or endoscopic remission after adjusting for confounding variables including age, sex, smoking status, baseline disease activity, concomitant corticosteroids, concomitant immunomodulators.

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:

• Trials of golimumab in ulcerative colitis (C0524T17, C0524T18)
• Trial of infliximab in ulcerative colitis (C0168T37, C0168T46, C0168T72)
Inclusion criteria:
• Patients (adults or pediatric) with moderate-severe ulcerative colitis (defined as Mayo Clinic score [MCS] of 6 to 12 points, with an endoscopic sub-score of 2 or 3)
• Treated with infliximab or golimumab or placebo for induction and/or maintenance
• Reported concomitant use or non-use of 5-ASA at time of screening or first study-related visit

Exclusion criteria
• Lack of information on use of 5-ASA at time of screening or first study-related visit
• Patients lost to follow-up or did not participate in trial after randomization (without receiving any dose of the medication)

Main Outcome Measure and how it will be categorized/defined for your study:

• Primary outcome – clinical remission (MCS?2, with no individual sub-score exceeding 1) after induction therapy (4-12 weeks) or after maintenance therapy (week 24-60)
• Secondary outcomes – clinical response (decrease in MCS by ?3 points and 30%, with decrease in the rectal bleeding sub-score by ?1 point, or an absolute sub-score of 0 or 1); mucosal healing (absolute endoscopy sub-score on MCS of 0 or 1)

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

Main predictor/independent variable will be concomitant use vs. non-use of 5-ASA.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

Key confounding variables of interest in our study are:
o Biochemical measures of disease severity – baseline C-reactive protein as a categorical variable (<0.5mg/dl or ?0.5mg/dl), fecal calprotectin (where available, <150mcg/g vs. ?150mcg/g)
o Co-interventions – concomitant use of immunomodulators like azathioprine, 6-mercaptopurine or methotrexate (yes vs. no), concomitant use of steroids (yes vs. no)
o Factors known to modify pharmacokinetics of anti-TNF therapy – baseline albumin as a categorical variable (<3.5g/dl vs. ?3.5g/dl), sex (males vs. females)
o All analysis will be stratified by age group of participants (adults vs. children); trials of induction and maintenance therapy will be analyzed separately

Statistical Analysis Plan:

Descriptive analysis: We will report proportions to present distribution of demographic, clinical and biochemical characteristics of participants stratified by concomitant use of 5-ASA or not, and calculate differences between groups using chi-square tests.
Univariate analysis: To assess how concomitant use of 5-ASA may modify response to anti-TNF therapy, we will pool data from active agent arms of all included trials. In this, we will estimate whether concomitant 5-ASA influences response to therapy by comparing proportion of patients achieving primary and secondary outcomes by baseline use vs. non-use of 5-ASA; IFX and GLM trials will be analyzed separately.
Multivariable analysis: To evaluate the impact of concomitant 5-ASA use independently on response to therapy in IBD, we will perform logistic regression analysis after adjusting for confounding variables including age, sex, smoking status, baseline disease activity, concomitant corticosteroids, concomitant immunomodulators.

Project Timeline:

Once study is approved and data access provided (assuming by December 2015), our key milestones dates are:
o Project start date: October 1, 2017
o Analysis completion date: October 31, 2017
o Manuscript drafted: December 31, 2017
o Manuscript submitted for publication: January 31, 2018
o Date results reported back to YODA: January 31, 2018

Dissemination Plan:

We anticipate generation of one manuscript from this project on the impact of concomitant 5-ASA use on treatment outcome. The target audience would be clinical gastroenterologists. Potentially suitable journals for this manuscript would be: Gastroenterology, Gut, American Journal of Gastroenterology, Inflammatory Bowel Diseases.

Bibliography:

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