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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/coi_-_dulaips.pdf
http://yoda.yale.edu/system/files/coi_-_singhs_0.pdf
http://yoda.yale.edu/system/files/coi_-_proudfootja_0.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. [NCT00537316 - Efficacy & Safety of Infliximab Monotherapy Vs Combination Therapy Vs AZA Monotherapy in Ulcerative Colitis (Part 1) Maintenance Vs Intermittent Therapy for Maintaining Remission (Part 2)](#)

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

Research Proposal

Project Title

Development of a Clinical Prediction Tool for Treatment Outcomes in Infliximab-treated Patients with Moderate-Severe Ulcerative Colitis

Narrative Summary:

Several biologic and small molecule therapies are available for the management of patients with moderate-severe ulcerative colitis (UC). However, there is limited data to inform optimal positioning and personalization of these therapies. We propose to identify factors predictive of response to infliximab, develop a prediction model and transform it into a simple to use prognostic clinical decision support tool to identify patients most, and least, likely to respond to these therapies. To develop the model, we will analyze phase III, placebo-controlled trials of infliximab in UC.

Scientific Abstract:

Background: Clinical decision support tools Clinical prediction models provide insight into the impact of patient characteristics on treatment outcomes, allowing for a more personalized treatment.
Objective: To identify factors predictive of response to infliximab (IFX), develop a prediction model and transform it into a clinical decision support tool to identify patients most, and least, likely to respond to these therapies
Study Design: Individual participant level pooled analysis of RCTs of IFX in patients with UC
Participants: Patients enrolled in phase III RCTs of IFX in moderate-severe UC
Main Outcome Measures: Clinical remission, endoscopic remission, and deep remission (clinical remission + endoscopic remission) at week 30
Statistical Analysis: We will use multivariable logistic regression to develop models predicting each of the three outcomes at week 30, then transform it into a single model, and develop a simple to use clinical decision support tool, by multiplying the ? coefficient by 10 and rounding to the nearest value. Overall performance of the models was evaluated using area under the ROC curve. This model will then be validated in an external real-world cohort, outside of the YODA platform.

Brief Project Background and Statement of Project Significance:

Several biologic and small molecule therapies are available (or anticipated to be available soon) for the management of patients with moderate-severe UC. However, there is limited data to inform optimal positioning and personalization of these therapies. Clinical prediction models utilize baseline characteristics to provide an estimate of the value of a therapy on treatment outcomes for an individual patient. Furthermore, the transformation of these models into decision support tools facilitates their application as a component of 'precision medicine'. With the evolving landscape of biologic therapy in UC and increasing treatment choice, a validated prognostic tool for treatment outcomes with IFX would be of considerable value. We aim to address this gap by deriving and validating a multivariable clinical prediction model within the ACT-1 and ACT-2 clinical trial dataset. To improve the ease with which this prediction model can be used at the 'bedside', we will transform it into a prognostic clinical decision support tool (CDST) and validated this tool in a cohort of UC patients treated with IFX in routine clinical practice. We have created a similar CDST to inform use of vedolizumab in patients with moderate-severe UC.
The significance of this work lies in developing and validating an easy-to-use CDST to identify patients with moderate-severe UC most, and least, likely to respond to infliximab. The information generated through this study would be invaluable to inform both science and patient care. From a scientific perspective, it will help identify clinical factors associated with response to infliximab, which can then be used to further understand how these

drugs may be effective. From a clinical perspective, information generated from this study on treatment response to infliximab, will be generalizable and directly applicable to patient care, informing clinical guidelines and offering potential for promoting value-based in patients with UC.

Specific Aims of the Project:

Specific aim #1: To identify factors predictive of response to infliximab in patients with UC, through post-hoc analysis of phase III RCTs of IFX in UC.
Specific aim #2: To develop (and subsequently) validate a prediction model to identify patients with UC most, and least, likely to respond to IFX.
Hypothesis: Short disease duration, lower inflammatory burden and higher albumin are associated with increased likelihood of response to infliximab

What is the purpose of the analysis being proposed? Please select all that apply.
Research on clinical prediction or risk prediction

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

Data sources:
• 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 placebo for induction and/or maintenance
Exclusion criteria
• 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) at week 30
• Secondary outcomes – clinical remission at week 8, endoscopic remission at week 8 and 30 (absolute endoscopy sub-score on MCS of 0 or 1), steroid-free remission at week 30

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

• Main predictor/independent variable will be exposure to IFX vs. placebo

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 (<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), dose of infliximab
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), weight
o Disease factors – disease extent (extensive colitis vs. left-sided colitis), disease duration

Statistical Analysis Plan:

A multivariable logistic regression prediction model will be built in the ACT-1 and -2 for the outcome of clinical remission at week 30. All baseline variables found to have a p value <0.15 on univariable analyses will be included in the multivariable model, after an assessment for co-linearity and clinical importance or interpretability, and a backward model selection approach will be used with a p value threshold of 0.15 for inclusion in the final model. Interaction terms will be assessed individually and included in the final model if they have a p value of < 0.10 on

univariable and multivariable analyses.

This model will then undergo external validation in the consortium established by Dr. Dulai (outside the YODA platform). Discriminative ability will be assessed by receiver operating characteristic (ROC) curve analysis and presented as area under the ROC curve (AUC). Calibration will be tested by the Hosmer–Lemeshow goodness-of-fit test after splitting the sample into quintiles. This test assesses whether or not the observed event rates match expected event rates in subgroups of the model population, with P-values <0.05 indicating evidence of poor fit. The overall performance of the models will be evaluated with the Nagelkerke R2 and the Brier score. Nagelkerke R2 is a measure between 0 and 1, with 0 denoting that the model does not explain any variation and 1 denoting that it perfectly explains the observed variation. The Brier score is a measure between 0 and 1 of prediction with the mean squared difference between the predicted probability and the actual outcome. A lower Brier score indicates better performance, and the Brier score for a model can range from 0 for a perfect model to 0.25 for a non-informative model.

The final prediction model will then transformed into a CDST by multiplying the ? regression coefficient of each predictor in the model by a factor of 10, rounding to the nearest value, and removing the intercept. The ACT-1 and -2cohort subjects will then be split into quartiles using the CDST, and cut-points will be determined for patients who have a low (lowest quartile of clinical remission rates), intermediate (middle two quartiles of clinical remission rates), or high (highest quartile of clinical remission rates) probability of responding to IFX. These cut-points will then be applied to the ACT-1 and -2 population to understand how the probability of achieving clinical remission with IFX compared with placebo-treated participants.

Finally, the CDST cut-points will be applied to the real-world consortium, and the sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of the scoring tool will be calculated to identify patients who had a low or high probability of achieving clinical remission with IFX.

Project Timeline:

o Project start date: June 1, 2018
o Analysis completion date: November 1, 2018
o Manuscript drafted: January 1, 2019
o Manuscript submitted for publication: January 31, 2019
o Date results reported back to YODA: January 31, 2019

Dissemination Plan:

We anticipate generation of one manuscript from this project on the development and validation of a clinical prediction model for response to infliximab in patients with UC. 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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