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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

Conflict of Interest

https://yoda.yale.edu/system/files/sv_6m4tghhxg7w7uxe-r_1iis1gpxfdjqgeo.pdf
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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

1. [NCT00036439 - C0168T37 - A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients With Active Ulcerative Colitis](#)
2. [NCT00096655 - C0168T46 - A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients With 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

A Prediction Model for Loss of Response in Ulcerative Colitis Patients Initially Responding to Infliximab Therapy After Induction.

Narrative Summary:

In the ACT-1/2 randomized controlled trials, infliximab (IFX) was superior to placebo in improving patients' symptoms and inflammation on colonoscopy(1). Many patients who symptomatically improved at week #8 of therapy often either flared or never reached symptomatic remission or resolution of inflammation on colonoscopy (mucosal healing) at week #30 of therapy(1,2). We aim to identify factors that predict whether patients with symptom improvement at week #8 of IFX therapy in the ACT-1/2 trials, will ultimately achieve symptomatic remission and resolution of inflammation on colonoscopy at week #30. This model will allow clinicians to identify patients at risk to lose response.

Scientific Abstract:

Background:

In the ACT-1/2 trials, infliximab (IFX) was proven superior to placebo in achieving clinical response at week #81, however, a significant proportion of those patients did not sustain their response or never reached clinical or endoscopic remission at weeks #30 or #54.

Objective:

To identify predictors amongst clinical responders at week #8 of IFX and develop a predictive model using variables at the beginning of maintenance therapy for lack of remission at week #30.

Study Design:

Post-hoc analysis of randomized controlled trials ACT-1/2.

Participants:

Patients who received IFX 5mg/kg or 10mg/kg and were clinical responders at week #8 and entered the maintenance phase of the trial.

Main Outcome Measures

Main outcome for model training and testing: Lack of remission at week #30. Remission is defined as a total Mayo score of ≤2 points, with no individual sub-score exceeding 1 point.

Secondary outcomes to test the predictive model on: lack of mucosal healing (defined as an absolute mayo

endoscopic sub-score of ?2); lack of remission at week #54 in the ACT-1 trial.

A web-based calculator will be developed based on the finalized model.

Statistical Analysis

Descriptive statistical tests will include t-tests/Mann-Whitney and chi-square tests for continuous and categorical variables, respectively. Machine learning (ML) univariable analysis and other embedded ML methods will be utilized for identifying useful predictors and finally the assembled predictive model's performance will be assessed with internal and external validation. Both histology and endoscopic evaluations at week #8, in addition to infliximab drug concentrations at week #14 and #22, and changes in drug concentrations between week #14 and #22, will be assessed using (log-) linear and quantile regression analyses.

Brief Project Background and Statement of Project Significance:

In the ACT-1/2 trials, infliximab (IFX) was proven superior to placebo in achieving clinical response at week #8, as well as at subsequent timepoints, including outcomes of clinical remission and endoscopic healing¹. Previous calculators predicting week #8 and week #30 endoscopic healing have been published³ using factors incorporating variables prior to treatment initiation in addition to pharmacokinetic variables. A separate and common dilemma exists amongst patients who respond to therapy but subsequently lose response. Previous models do not account for this common scenario, for which it is difficult to identify in whom this will occur. Consistent with this experience, in the ACT trials, a significant proportion of clinical responders at week #8 did not sustain their response or never reached remission^{1, 2}. In addition, important novel information such as histology has not yet been incorporated into these predictive models.

We aim to study clinical responders to IFX at week #8, identify predictors and predict the risk of not being in remission at Week #30. We will also aim to identify if this model can predict MH at week #30 and remission at week #54. The model is planned to be converted to a web-based, easily accessible calculator, for clinic or bedside use.

Additionally, we aim to identify cutoffs of IFX trough levels at weeks #14 and #22 associated with the outcome.

The findings of this study will aim to elucidate drivers of remission (or lack thereof) in patients who had initial clinical response to infliximab at week #8. These findings will collectively enable clinicians to answer the question of which initial IFX responders are likely to need a closer follow-up, proactive monitoring and overall prognostication of 1-year outcomes.

Specific Aims of the Project:

Our primary aim is to identify high-yield predictors and build a robust predictive model that can accurately predict lack of remission at week #30 in patients with moderate-to-severe ulcerative colitis that have clinically responded by week #8 of infliximab.

Secondary aims include assessment of model performance for predicting lack of mucosal healing at week #30 and lack of remission at week #54. An exploratory analysis in the ACT 1 trial patients will be performed for both individual and aggregate (median, mean) infliximab trough levels from weeks #38 and #46 and #54 since first maintenance dose (week 14), as well as identifying optimal cutoff levels at those weeks with AUC analysis.

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

Confirm or validate previously conducted research on treatment effectiveness

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:

The ACT-1 and ACT-2 trial datasets will be used to extract patients with the following inclusion/exclusion criteria:

Include if:

- Received infliximab (5mg/kg or 10mg/kg) throughout at least until week #54, and
- Deemed as clinical responders on Week #8

And exclude if any of the following:

- Deviated from protocol (Infliximab stopped for any reason)
- Missing Week #30 endoscopy data (outcome)
- Missing Week #14 drug level or antibody-to-infliximab status

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

The main outcome is the prediction of lack of remission at week #30, among patients who were clinical responders at week #8.

Secondary aims include assessment of model performance for mucosal healing at week #30 and remission at week #54. An exploratory analysis in the ACT-1 trial patients will be performed for both individual and aggregate (median, mean) infliximab trough levels from weeks #38 and #46 and #54 since first maintenance dose (week 14), as well as identifying optimal cutoff levels at those weeks with AUC analysis that are associated with lack of endoscopic healing at week #54.

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

Demographic Predictors:

- o Gender, Age, Race/Ethnicity
- o Current smoker

Clinical Predictors:

- o Anthropometric: weight, height, BMI
- o Disease extent (proctitis-only / left colitis / proximal to splenic flexure)
- o Disease duration
- o Steroid refractory upon randomization
- o Immunomodulator (IMM) use at baseline
- o Stool frequency (at weeks #8, #14, #22)
- o Rectal bleeding score (RBS; at weeks #8, #14, #22)
- o Partial Mayo score (pMayo; at weeks #8, #14, #22)

Laboratory Predictors:

- o CBC components (at weeks #0, #14, #22): Hemoglobin, MCV, MCHC, MCH, WBC, Neutrophils, Monocytes, Basophils, Eosinophils, Platelets.
- o Serum Albumin (at weeks #0, #14, #22). Cutoff analysis for Week #14 and Week #22, based on area-under-the curve.
- o Infliximab drug level (at weeks #14, #22).
- o Infliximab antibodies (AUC cutoff analysis, binary yes/no)
- o Infliximab clearance at baseline (based on 4)
- o C-reactive protein (CRP), Erythrocyte Sedimentation Rate (ESR), Fecal calprotectin (FCP) at weeks #0, #8, #14, #22.

Endoscopy/Histology Predictors:

- o Mayo endoscopic score (MES) and endoscopic healing at week #8.
- o Geboes Score, Histologic remission (Geboes 2B.0, Geboes 3, 4, 5 =0) at week #8

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

All variables above will be initially equally considered and then analyzed based on various machine learning (ML) algorithms to establish correlation with the outcome and finally shortlisted for use in the multivariable predictive model.

Additionally-created features (predictors) to be examined:

Clinical Predictors:

- o ? stool frequency week #22 – week #8
- o ? RBS week #22 – week #8
- o ? pMayo week #22 – week #8

Laboratory Predictors:

- o ? of week #22 - week#14 for: CBC components Hemoglobin, MCV, MCHC, MCH, WBC, Neutrophils, Monocytes, Platelets.
- o ? serum Albumin of week #22 – week #14
- o ? infliximab serum drug level week #22 – week #14.
- o ? week #14 - #0 and week #22 - #14 for CRP, ESR, FCP.

Statistical Analysis Plan:

To minimize miss-specification and given the sample size of ACT-1, and ACT-2, we are not planning to impute missing values, therefore rows with missing values from any potential predictor will be excluded.

Descriptive and bivariate analysis (t-test, chi-square testing, Mann-Whitney test) between week #8 clinical responders who had remission vs. those who had not, by week #30.

Predictor identification for lack of remission at week #30 will be done systematically using statistical and ML-based algorithms including, predictive power score(5) (using 5-fold cross-validation, based on univariable F1 score analysis) and multivariable techniques such as information value, random forest, recursive feature elimination, extra trees, chi-square, L-one score – all scores contribute up to 1 vote from each algorithm based on whether it predicts the outcome better than chance. Predictors with variance inflation factor > 10 will be excluded to minimize multicollinearity. Finally, the potential predictors will be processed via the Maximum Relevance-Minimum Redundancy (MRMR) algorithm(6). The final predictors will be evaluated by the investigators for biological plausibility and based on prior findings from the literature.

The ML algorithms, depending on available sample size, will be internally validated using nested repeated (x5) 5-fold cross-validation(7), allowing for hyperparameter tuning with minimized bias. The algorithms' performance will be evaluated based on F1 and AUC scores. External validation will be done on the best-performing algorithm. The ML algorithms planned to be trained and tested include logistic regression, logistic regression with regularization (L1/L2), gradient boosting classifier(8), XGBoost(9) and QLattice(10).

Cutoff analysis for maximal sensitivity and specificity of the various maintenance-period IFX trough levels, will be done by analyzing AUC and geometric mean of sensitivity and specificity.

Predictors of median and mean IFX trough levels during the maintenance period will be checked based on log-transformed and quantile regression, respectively.

Software Used:

Python

Project Timeline:

Project start date: 3/1/2022 (tentative; pending YODA acceptance)

Analysis completion date: 4/1/2022

Date of manuscript draft completion and first submitted for publication: 5/1/2022

Date for results reported back to YODA project: 5/1/2022 or after first conditional acceptance by a Journal, depending on peer-review commentary

Dissemination Plan:

We aim to provide a web-accessible online calculator, based on a robust predictive model, that can be used on-demand at the clinic or bedside. Our target audience is clinical and research-oriented Gastroenterologists and enable them to predict whether an early clinical responder to infliximab will have lack of remission at week #30. Depending on the strength of the study's findings, journals we have under consideration for submission include Gastroenterology, Clinical Gastroenterology & Hepatology, American Journal of Gastroenterology, Journal of Crohn's & Colitis, and Alimentary Pharmacology and Therapeutics.

Bibliography:

1. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005;353:2462-76.
2. Colombel JF, Rutgeerts P, Reinisch W, et al. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. *Gastroenterology* 2011;141:1194-201.
3. Vande Casteele N, Jairath V, Jeyarajah J, et al. Development and Validation of a Clinical Decision Support Tool That Incorporates Pharmacokinetic Data to Predict Endoscopic Healing in Patients Treated With Infliximab. *Clin Gastroenterol Hepatol* 2021;19:1209-1217 e2.
4. Vande Casteele N, Jeyarajah J, Jairath V, et al. Infliximab Exposure-Response Relationship and Thresholds

Associated With Endoscopic Healing in Patients With Ulcerative Colitis. *Clin Gastroenterol Hepatol* 2019;17:1814-1821 e1.

5. Wetschoreck F, Krabel T, Krishnamurthy S. 8080labs/ppscore: zenodo release. 2020.

6. Peng H, Long F, Ding C. Feature selection based on mutual information criteria of max-dependency, max-relevance, and min-redundancy. *IEEE Transactions on Pattern Analysis and Machine Intelligence* 2005;27:1226-1238.

7. Cawley GC, Talbot NLC. On over-fitting in model selection and subsequent selection bias in performance evaluation. *The Journal of Machine Learning Research* 2010;11:2079-2107 @ 1532-4435.

8. Pedregosa F, Varoquaux G, Gramfort A, et al. Scikit-learn: Machine Learning in Python. *Journal of Machine Learning Research* 2011;12:2825-2830.

9. Chen T, Guestrin C. XGBoost: A Scalable Tree Boosting System, In 22nd ACM SIGKDD International Conference on Knowledge Discovery and Data Mining, New York, NY, USA, ACM, 2016.

10. Abzu. Feyn software. 2.1 ed: Abzu, 2021.