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General Information

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SCOPUS ID:
Requires Data Access? Yes

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

https://yoda.yale.edu/wp-content/uploads/2017/02/coi-shenghong_zhang.pdf
https://yoda.yale.edu/wp-content/uploads/2017/08/coi-rirong_chen.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

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
3. NCT00487539 - C0524T17 - 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
4. NCT00488631 - C0524T18 - 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
5. NCT00488774 - C0524T16 - A Phase 2/3 Multicenter, Randomized, Placebo-controlled, Double-blind Study to Evaluate the Safety and Efficacy of Golimumab Induction Therapy,

Administered Intravenously, in Subjects With Moderately to Severely Active Ulcerative Colitis

6. NCT02407236 - CNTO1275UCO3001 - A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Protocol to Evaluate the Safety and Efficacy of Ustekinumab Induction and Maintenance Therapy 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

Biomarkers for predicting long-term outcomes in ulcerative colitis

Narrative Summary:

Ulcerative colitis (UC) is a chronic inflammatory disease with an increasingly incidence worldwide. Patients with UC have heterogenous prognosis: some patients have good long-term outcomes after initiation treatment, while some will suffer from relapsing and exacerbated disease courses. Therefore, predicting the prognosis of UC patients is important for selecting optimal treatment approaches and conducting personalized management. Biomarkers are non-invasive, easy-available and promising indicators for assessing disease activity and predicting prognosis in UC. In this project, we will perform post-hot analysis and identify useful biomarkers for predicting long-term outcomes in UC.

Scientific Abstract:

Background: Ulcerative colitis (UC) is a chronic inflammatory disease with an increasingly incidence around the world. Patients with UC have heterogenous prognosis which hamper the selection of optimal treatment.
Objective: The primary objective of this study is to investigate the relationship between potentially useful biomarkers and long-term outcomes, such as endoscopic remission, histological remission and colectomy.
Study Design: This is a post hoc analysis including three clinical trials (UNIFI, PURSUIT and ACT) from the Yoda project and six trials from the Vivli platform. Faecal calprotectin and faecal lactoferrin are major predictors. Other biomarkers like C-reactive protein, albumin and haemoglobin are also evaluated. This study will analyse the predictive ability of candidate biomarkers for long term outcomes.
Participants: Patients who received biologics will be included in this study. Participants who meet any of the following criteria are not eligible for study inclusion: receiving placebo during the course of the induction or maintenance study; lacking data of corresponding predictors during induction therapy.
Main Outcome Measure(s): Endoscopic remission of endpoints is the primary outcome in this study and assessed by mayo endoscopic score. Secondary outcomes include clinical remission, histological remission, endoscopic and histological improvement, and colectomy.
Statistical Analysis: Multivariate logistic regression or cox regression will be used to assess the relationship between candidate biomarkers and the likelihood of achieving long-term outcomes, after adjusting for confounders. The receiver operating characteristic (ROC) analysis is performed to assess the predictive ability of candidate biomarkers. Subgroup analysis by treatment allocation, disease activity at baseline, age and gender will be performed.

Brief Project Background and Statement of Project Significance:

Ulcerative colitis (UC) is a chronic inflammatory disease affecting around 2% of the general population in North America and Western Europe, and its incidence is rising worldwide [1, 2]. Patients with UC have varying prognosis: some patients have good long-term outcomes after initiation treatment, while some will suffer from relapsing and worsening disease [3, 4]. Therefore, predicting the prognosis of UC patients is important for selecting the best treatment approaches and conducting personalized management. Nowadays, identifying effective indicators for predicting the prognosis in UC is receiving considerable attention. Biomarkers (biological molecules found in blood, other body fluids, or tissues) are non-invasive, easy-available and promising indicators for assessing disease activity and predicting prognosis in UC [5]. This study aims at identifying useful biomarkers and investigating their predictive ability for long-term outcomes in UC.

Specific Aims of the Project:

This study aims at investigating the association between candidate biomarkers and long-term outcomes, such as endoscopic remission, histological remission and colectomy, in UC patients. Moreover, the ability of candidate biomarkers for predicting long-term outcomes will be analysed. The scientific hypothesis of this study is that biomarker concentration can reflect inflammation condition and indicate long-term outcomes in UC.

Study Design:

Individual trial analysis

Research Methods

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

The source of the data will be from UNIFI, PURSUIT (PURSUIT-SC, PURSUIT-IV and PURSUIT-M), ACT (ACT 1 and ACT 2) from the Yoda Project and other six trials (study ID: NCT00783718, NCT02497469, NCT00385736, NCT00408629, NCT00790933 and NCT02611830) from the Vivli platform.
Patients who received biologics will be included in this study. Participants who meet any of the following criteria are not eligible for study inclusion: receiving placebo during the course of the induction or maintenance study; lacking data of corresponding predictors during induction therapy.

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

The primary outcome is endoscopic remission at the end of maintenance therapy. Endoscopic remission is a dichotomized variable and defined as mayo endoscopic score equal to 0. Secondary outcomes include endoscopic improvement, histological remission, histological improvement, clinical remission at the end of maintenance therapy. All these outcomes are dichotomized variables. Endoscopic improvement is defined as mayo endoscopic score

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

The main predictors of this study include faecal calprotectin and faecal lactoferrin at different time, such as baseline, week 2, 4, end of induction. Concentration of faecal calprotectin and faecal lactoferrin will be analysed as continuous variables.

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

Other variables of interest include potential biomarkers, such as c-reactive protein, albumin, haemoglobin, neutrophils, lymphocytes, platelet and so on, disease activity at baseline, age, gender, treatment allocation, concomitant therapy, disease duration, disease location, disease behaviour,

prior biologic exposure. Continuous variables and categorized variables will be described as median (interquartile range) and proportion (percentage), respectively.

Statistical Analysis Plan:

Continuous and categorical variables are described as median (interquartile range, IQR) and proportion (percentage), respectively. The Mann-Whitney test and ?2 test were performed to evaluate the difference for continuous and categorical variables, respectively. A p-value less than 0.05 was considered as statistical significance. Univariate logistic or cox regression analysis will be conducted to analyse the association of candidate predictors and outcomes. Multivariate logistic or cox regression analysis will be performed to adjusted potential confounders (like disease duration, treatment allocation). The receiver operating characteristic (ROC) analysis is performed to calculate the area under ROC curve (AUROC). The cut-off value is determined by the Youden index. AUROC, sensitivity, specificity, positive predictive value and negative predictive value are used to assess the predictive capacity of the predictors for predicting specific outcomes. Furthermore, we will perform subgroup analyses by treatment allocation, disease activity at baseline, age and gender. Missing value for major outcome will be excluded from statistical analysis. Missing values for other variables will be imputed by simple imputation, using the mice package in R.
Taking account of differences among studies, we will (1) compare baseline characteristics, like age, sex, race, disease duration and disease activity, among different trails. If some covariates are found different among trials, we will adjust them in the multivariate regression model; (2) perform subgroup analysis stratified by different trials to assess the interaction between predictors and trials; (3) conduct sensitivity analyses in patients with same disease activity, range of age, disease duration or type of biologics (anti-TNF agents, vedolizumab or ustekinumab) to verify the consistency of our results.

Project Timeline:

Start date - June 2022
Analysis completion date - January 2024
Manuscript draft - February 2024
Submitted for publication - March 2024

Dissemination Plan:

The products of this project will be submitted to scientific conference, such as Digestive Disease Week, European Crohn?s and Colitis Organization and Asian Crohn?s and Colitis Organization. The manuscripts will also be submitted for publication in peer-reviewed journals. Clinical Gastroenterology and Hepatology (CGH), Journal of Crohn's and Colitis (JCC), American Journal of Gastroenterology (AJG) and Inflammatory Bowel Diseases (IBD) would be possible the journals of choice for our plan. The acknowledgement for the Yoda Project will be presented in all products of this study.

Bibliography:

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