Principal Investigator

First Name: Rirong
Last Name: Chen
Degree: Dr
Primary Affiliation: The first affiliated hospital of Sun Yet-sen University
E-mail: chenrr9@mail2.sysu.edu.cn
Phone number:
Address:

City: Guangzhou
State or Province: Guangdong
Zip or Postal Code: 510000
Country: China

General Information

Key Personnel (in addition to PI):

First Name: Rirong
Last name: Chen
Degree: MD
Primary Affiliation: The First Affiliated Hospital of Sun Yat-sen University
SCOPUS ID:

First Name: Shenghong
Last name: Zhang
Degree: MD,PhD
Primary Affiliation: The First Affiliated Hospital of Sun Yat-sen University
SCOPUS ID:

First Name: Yizhie
Last name: Tie
Degree: MD
Primary Affiliation: The first affiliated hospital of Sun Yet-sen University
SCOPUS ID:

First Name: Jieqi
Last name: Zheng
Degree: MD
Primary Affiliation: The first affiliated hospital of Sun Yat-sen university
SCOPUS ID:

Are external grants or funds being used to support this research?: External grants or funds are being used to support this research.
Project Funding Source: National Natural Science Foundation of China, grant/award number: 82070538 and 81870374.
How did you learn about the YODA Project?: Scientific Publication

Conflict of Interest

https://yoda.yale.edu/system/files/coi-rirong_chen_0.pdf
https://yoda.yale.edu/system/files/coi-shenghong_zhang_0.pdf
https://yoda.yale.edu/system/files/coi_form_yt.pdf

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https://yoda.yale.edu/system/files/coi_form_jz.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: This study aims at investigating the prognostic value of candidate biomarkers and long-term outcomes in patients with UC.

Study Design: This is a post hoc analysis including three clinical trials (UNIFI, PURSUIT and ACT). Faecal calprotectin and faecal lactoferrin are major predictors. Other biomarkers like C-reactive protein, albumin and

haemoglobin are also evelauted. This study will analyse the predictive ability of candidate biomarkers for long term outcomes.

Participants: Patients who completed an induction study and participate in the maintenance study will be included.

Main Outcome Measure(s): The primary outcome is endoscopic remission at the end of maintenance therapy. Secondary outcomes include endoscopic improvement, histological remission, histological improvement, clinical remission and colectomy.

Statistical Analysis: Multivariate logistic and 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 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 heterogenous prognosis: some patients have good long-term outcomes after initiation treatment, while some will suffer from relapsing and exacerbated disease courses.[3,4] Therefore, predicting the prognosis of UC patients is important for selecting optimal treatment approaches and conducting personalized management. Nowadays, identifying effective indicators for predicting the prognosis in UC is receiving considerable attention. Biomarkers 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. This analysis will include data from three clinical trials (UNIFI, PURSUIT and ACT1/2). The primary objective of this study is to investigate the relationship between candidate biomarkers and long-term outcomes, such as endoscopic remission, histological remission and colectomy. 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. The results will explore useful biomarkers and may help in selecting treatment approaches for patients with different prognosis 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.

What is your Study Design?:

Individual trial analysis

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:

The source of the data will be from UNIFI, PURSUIT (PURSUIT-SC, PURSUIT-IV and PURSUIT-M) and ACT (ACT 1 and ACT 2). Patients who completed an induction study and participate in the maintenance study will be included.

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 <2. Histological remission and histological improvement are defined as Geboes highest grade <2.0 and <3.2, respectively. Clinical remission is defined as partial mayo score <3 and no subscore > 1 on any of the four parameters. Colectomy during follow-up is also a secondary outcome.

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 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.
Software Used:
RStudio
Project Timeline:

Start date - December 2022
Analysis completion date - March 2023
Manuscript draft - May 2023
Submitted for publication - August 2023

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. A manuscript will also be submitted for publication in peer-reviewed journals. The acknowledgement for YODA Project will be presented in all products of this study.

Bibliography:

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