Principal Investigator

First Name: Shenghong
Last Name: Zhang
Degree: M.D.
Primary Affiliation: Department of Gastroenterology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China
E-mail: shenghongzhang@163.com
State or Province: Guangzhou
Country: China

General Information

Key Personnel (other than PI):
First Name: Jieqi
Last name: Zheng
Degree: M.D.
Primary Affiliation: Department of Gastroenterology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China
SCOPUS ID:
Requires Data Access? Yes

First Name: Rirong
Last name: Chen
Degree: M.D.
Primary Affiliation: Department of Gastroenterology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China
SCOPUS ID:
Requires Data Access? Yes

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How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2024/04/COI-Shenghong_Zhang.pdf
https://yoda.yale.edu/wp-content/uploads/2024/04/COI-Jieqi_Zheng.pdf
https://yoda.yale.edu/wp-content/uploads/2024/04/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. NCT01369329 - CNTO1275CRD3001 - A Phase 3, Randomized, Double-blind, Placebo-

controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Subjects With Moderately to Severely Active Crohn's Disease Who Have Failed or Are Intolerant to TNF Antagonist Therapy (UNITI-1)

2. NCT01369342 - CNTO1275CRD3002 - A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Subjects With Moderately to Severely Active Crohn's Disease (UNITI-2)
3. NCT01369355 - CNTO1275CRD3003 - A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Maintenance Therapy in Subjects With Moderately to Severely Active Crohn's Disease

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

Research Proposal

Project Title

Dynamics of Disease Activity in Monitoring Therapeutic Outcomes and Predicting Prognosis for Crohn’s disease

Narrative Summary:

Crohn's disease(CD) is a chronic, recurrent inflammatory bowel disease. Recent years have witnessed a surge in the development of targeted therapies such as biologics, while not all CD patients could benefit from targeted therapies. Thus, timely monitoring disease activity and predicting therapeutic response are vital during therapies. Describing trajectories of disease course is a promising topic in current clinical research, while relatively limited studies towards this have been reported in CD patients with biological therapies. Therefore, we aim to investigate the role of disease activity dynamic trajectories in therapeutic efficacy monitoring and prognosis predicting in CD.

Scientific Abstract:

Background: As the emergence of novel biologics, monitoring disease activity and predicting therapeutic efficacy has become essential processes in CD management. However, longitudinal dynamics of disease activity have not been fully understood.
Objective: This study aims to explore the trajectories of disease activity within one year of biologic therapy in CD patients to provide evidence for disease monitoring and personalized medicine.
Study design: This is a post-hoc analysis study including data from one or more of five clinical trials (VERSIFY, UNITI-1 , UNITI-2 , IM-UNITI, and EXTEND). Major predictors include dynamics of disease activity within follow-up time.
Participants: Moderate-to-severe CD patients with at least three time of disease activity assessment would be included. Participants who meet any of the following criteria are not eligible for study inclusion: lacking data of corresponding predictors during induction therapy; having concomitant intestinal infection disease when assessing predictors after induction therapy.
Outcome Measure(s): Outcomes include post-maintenance therapeutic efficacy, such as clinical remission, mucosal healing, endoscopic improvement, patient-reported outcomes, etc.
Statistical analysis: The latent class growth mixed model is performed to fit the trajectory of disease activity. Cross-lagged structural equation models are used to explore temporal relationships of the predictors. Multivariate logistic regression is conducted to adjust potential confounders and to analyze the association of candidate predictor and outcomes.

Brief Project Background and Statement of Project Significance:

Crohn's disease(CD) is a chronic, recurrent inflammatory bowel disease. Recent years have witnessed a significant surge in the development of targeted therapies, which has expanded the therapeutic options for CD, such as adalimumab, ustekinumab, infliximab, and vedolizumab . Timely monitoring disease activity and predicting therapeutic response are vital processes during biologics and small molecules, especially in the initial year of treatment. However, for CD patients with targeted therapy, relatively limited studies describing trajectories of disease course have been reported. Therefore, in order to investigate the role of disease activity dynamic trajectories in therapeutic efficacy monitoring and prognosis predicting, we will perform post-hoc analysis based on one or more of the five randomized clinical trials, including VERSIFY, UNITI-1 , UNITI-2 , IM-UNITI, and EXTEND.

Specific Aims of the Project:

This study aims to explore distinct trajectories of disease activity within one year of targeted therapy in CD patients, so as to provide evidence for disease monitoring and personalized medicine. The scientific hypothesis of this study is that the trajectories of major predictors could help to monitor disease courses and predict different therapeutic outcomes in CD.

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:

Participants from one or more clinical trials (UNITI-1 , UNITI-2, and IM-UNITI from the YODA Project; VERSIFY and EXTEND from the Vivli Project) will be included in the study as either a development cohort for trajectory fitting or a external validation cohort. Moderate-to-severe CD patients with at least three time of disease activity assessment would be included. Participants who meet any of the following criteria are not eligible for study inclusion: lacking data of corresponding predictors during induction therapy; having concomitant intestinal infection disease when assessing predictors after induction therapy.

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

Outcomes include therapeutic efficacy (such as clinical response, clinical remission, mucosal healing, endoscopic response, patient-reported outcomes etc.) at the end of maintenance treatment, as well as colorectal resection during long-term follow-up.
Clinical response is defined as a decrease from baseline in the CDAI ≥100 points or a CDAI score <150. And clinical remission is defined as CDAI<150. As for endoscopic outcomes, endoscopic response is defined as Simple Endoscopic Score for CD(SES-CD) decrease ≥50% from baseline, while mucosal healing is defined as SES-CD 20 points and IBDQ ≥170 points, respectively.

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

The major predictors include clinical activity (e.g., CDAI), patient-reported outcomes(e.g., patient-reported outcome 2), serum and fecal biomarkers (e.g., C-reactive protein, hemoglobin, albumin,

and fecal calprotectin), endoscopic scores, patient report outcomes (e.g., IBDQ scores), and their long-term trajectories. They will be collected during one-year targeted treatment and before the end of maintenance therapy.

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 baseline characteristics (e.g., gender, age, disease duration, body mass index, medication history, treatment allocation and concomitant therapy) and baseline disease activity evaluation (e.g., CDAI, fecal calprotectin and C-reactive protein).

Statistical Analysis Plan:

Continuous and categorical variables are described as median (interquartile range) or frequency (percentage), respectively. The latent class growth mixed model (LCGMM) is performed to fit the trajectory of disease activity dynamic trajectory. LCGMM is a validated approach used to analyze longitudinal data and identify subgroups with distinct trajectories,which has been applied in various diseases. Based on lcmm package in R software, LCGMM usually uses linear, quadratic, or cubic polynomial functions with different class numbers ranging from 2 to 5 for identifying subgroups with distinct trajectories. The optimal trajectory was selected based on (1) the lowest Bayesian information criterion, (2) a minimum of 5% of patients in each class, and (3) the posterior probability of assignments being >0.7 in each class. Cross-lagged structural equation models are used to explore temporal relationships of the predictors. Multivariate logistic regression is conducted to adjust potential confounders (such as age, sex, medications, and baseline CDAI) and to assess whether variables of interest could independently predict outcomes. Statistical significance was set at p-value<0.05. All statistical analysis is performed via R software within the secure platform to which the YODA project or the Vivli project remote desktop is connected.

Software Used:

RStudio

Project Timeline:

Anticipated project start: 2024/7/15
Analysis completion: 2025/2/15
Manuscript drafted: 2025/2/15
First submitted for publication: 2025/3/15
Results reported back to the YODA Project: 2025/6/15

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, such as Clinical Gastroenterology and Hepatology (CGH), Journal of Crohn's and Colitis (JCC), American Journal of Gastroenterology (AJG) and Inflammatory Bowel Diseases (IBD) and others. The acknowledgement for Vivli Project and YODA Project will be presented in all products of this study.

Bibliography:

1. Dolinger, M., J. Torres and S. Vermeire, Crohn’s disease. Lancet, 2024. 403(10432): p. 1177-1191.
2. Liu, Y.H., et al., One-Year Trajectory of Cognitive Changes in Older Survivors of COVID-19 in Wuhan, China: A Longitudinal Cohort Study. JAMA Neurol, 2022. 79(5): p. 509-517.
3. Bui, D.S., et al., Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life. Lancet Respir Med, 2018. 6(7): p. 535-544.

4. Jia, J., et al., Biomarker Changes during 20 Years Preceding Alzheimer's Disease. N Engl J Med, 2024. 390(8): p. 712-722.
5. Constantine-Cooke, N., et al., Longitudinal Fecal Calprotectin Profiles Characterize Disease Course Heterogeneity in Crohn's Disease. Clin Gastroenterol Hepatol, 2023. 21(11): p. 2918-2927.e6.
6. Van Den Houte, M., et al., Predictors of symptom trajectory in newly diagnosed ulcerative colitis: a 3-year follow-up cohort study. J Crohns Colitis, 2024.
7. Chen, R., et al., Trajectory of fecal lactoferrin for predicting prognosis in ulcerative colitis. Precis Clin Med, 2023. 6(3): p. pbad022.