Principal Investigator

First Name: Shu-Chen
Last Name: Wei
Degree: doctor
Primary Affiliation: faculty
E-mail: scwei05@gmail.com
Phone number: +886905172116
Address: No.7, ZhongShan South Road., Zhongzheng Dist, Taipei City, Taiwan
No.7, ZhongShan South Road., Zhongzheng Dist
City: Taipei
State or Province: Taipei
Zip or Postal Code: 100
Country: Taiwan

General Information

Key Personnel (in addition to PI):
  First Name: Shu-Chen
Last name: Wei
Degree: Professor
Primary Affiliation: National Taiwan University Hospital
SCOPUS ID:

  First Name: Su-Yin
Last name: Lee
Degree:
Primary Affiliation: Dept of Internal Medicine, National Taiwan University Hospital
SCOPUS ID:

  First Name: Nai-Wen
Last name: Chang
Degree:
Primary Affiliation: National Taiwan University Hospital
SCOPUS ID:

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?: Data Holder (Company)

Conflict of Interest

https://yoda.yale.edu/system/files/conflict_of_interest_disclosure_scw_0_0.pdf
https://yoda.yale.edu/system/files/coi_syl.pdf
https://yoda.yale.edu/system/files/coi_nwchang.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

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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

Serum cytokines in predicting outcomes to ustekinumab in patients with Crohn's disease

Narrative Summary:

Pro-inflammatory cytokines play a key role in promoting mucosal inflammation. Biologics open a new era for the treatment of IBD, especially for Crohn's disease. TNF-a antibody is the first class to come to clinical practice, follow by integrin antibody, and more recently, we have the IL-12/23 antibody. Among them, none has 100% effectiveness. It is crucial to identify biomarkers that can predict and monitor therapeutic success in order to tailor individualized treatment strategies. As the above biologics are targeting at different proinflammatory cytokines, we hypothesize that different pro-inflammatory cytokine background might affect the treatment response to different class of biologics.

Scientific Abstract:

Background: Only certain subgroups of CD patients benefit to biologics,it is crucial to identify biomarkers that can predict treatment outcomes.Objective:To assess whether pre-treatment serum cytokines can predict the outcomes of ustekinumab treatment in CD patients. Study Design:This post-hoc analysis aims to evaluate if serum pro-inflammatory cytokine at baseline or early change of cytokine can predict the response to ustekinumab. Pro-inflammatory cytokines analyzed in UNITI-1 and UNITI-2 studies will be evaluated.Participants:Patients in UNITI-1 and UNITI-2 who received ustekinumab treatment will be included. Main Outcome Measure: To find the cut-off values of the examined pro-inflammatory cytokine level to predict clinical improvement (by CDAI) after receiving ustekinumab treatment. Statistical Analysis: Univariate linear regression will be used to assess the association of clinical improvement (?CDAI) between early change (week 3 and baseline), and change of CDAI at week 16 and week 52 of each cytokines level. The cytokine revealed a significant relationship with clinical improvement will be selected. Multivariable linear regression models will be used to confirm the association of selected cytokines and demographics with clinical improvement. The cytokines which show strongest predictive value in multivariate analyses will be selected in ROC analysis for finding optimal cut-off of cytokine level as predictor for clinical improvement. The predictive power of cytokine will be examined by calculating the area under the ROC curve.

Brief Project Background and Statement of Project Significance:

Biologics open a new era for the treatment of inflammatory bowel disease (IBD), especially for Crohn's disease (CD). Although several biologics with different mechanism have been approved in clinical use, none of them has 100% effectiveness. For example, the TNF-? antibody group, 30% of patients are primary non-responder [1, 2]. For integrin antibody, more than 50% patients did not achieve the clinical response [3]. And for IL-12/23 antibdoy, about 40% patients did not respond [4, 5]. Therefore, how to choose the most appropriate biologics for the most

appropriate patients is very important. In addition, how to sequence them becomes an important as well as a very practical issue [6].

Previously, clinical parameters have been evaluated as predictors of treatment outcomes. Genetic markers also have been evaluated. However, clinical parameters were not able to predict the outcomes [7]. Many genes have been explored, and despite some polymorphisms emerged with a great potential, particularly in members of the TNF family, the overall results are poor and no good predictive biomarkers for IFX or ADA response have been established [7, 8].

As a result, it is crucial to identify biomarkers that can predict and monitor therapeutic success in order to tailor individualized treatment strategies. As the above biologics are targeting at different proinflammatory cytokines, we hypothesize that different pro-inflammatory cytokine background might affect the treatment response to different class of biologics. Therefore, we would like to evaluate the pre-treatment cytokines as possible predictor of outcomes for ustekinumab (IL-12/23 antibody). With these results, we hope we can approach the aim as "right drug for right patients".

Specific Aims of the Project:

The primary aim of this study was to identify possible serum cytokine as biomarkers to predict the response to ustekinumab treatment in patients with Crohn Disease.

What is the purpose of the analysis being proposed? Please select all that apply.
Summary-level data meta-analysis using only data from YODA Project
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:

This study will utilize data from the Yale University Open Data Access (YODA) Project. Patients were eligible for UNITI-1, UNITI-2 and IM UNITI if they had moderate-to-severe CD and if they were failing conventional therapies or anti-TNF therapy. Among these studies, clinical response was collected at week8, week16 and week 52. Participants must meet all of the following criteria to be eligible for study inclusion : ?18 years of age, CD for at least 3 months, moderate-to-severe CD (defined as a CDAI score 220-450), nonresponse to anti-TNF therapy or treatment failure or intolerance to immunomodulators and/or glucocorticoids. Participants who meet any of the following criteria are not eligible for study inclusion: Bowel resection within 6 months, received infliximab, adalimumab or certolizumab pegol ?8 weeks before receiving study drug, ongoing chronic or recurrent infection, previously received a biologic agent targeting IL-12 or IL-23.

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

This study examines to which pro-inflammatory cytokine can be used to predict clinical improvement (by CDAI) after receiving ustekinumab treatment. It also examines the cut-off value of the cytokine level for predicting clinical outcome by ROC.

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

For this study, all pro-inflammatory cytokines which were analyzed in UNITI-1 and UNITI-2 studies will be evaluated. Include but not limit to following 12 cytokines which has been reported in literature: IL6 (pg/mL), IL17A (pg/mL), IL17F (pg/mL), IFN? (pg/mL), TNF? (pg/mL), MMP1 (ng/mL), MMP3 (ng/mL), MMP9 (ng/mL), MPO (pg/mL), SAA (ng/mL) , IL-22(pg/mL), IL-23(pg/mL).
Definition of Crohn's Disease Activity Index (CDAI) will be the same as in UNITI study.

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

Baseline patient demographic and clinical characteristics such as age, weight, sex, duration of disease, baseline CRP, baseline fecal calprotectin, steroid use, medication history etc. will be used to adjust regression models.

Statistical Analysis Plan:

To identify which cytokines are associated with clinical improvement (?CDAI), univariate linear regression will be performed to assess the association between each baseline cytokine level and ?CDAI after ustekinumab treatment. The association between early change (between week 3 and baseline) of each cytokine after treatment and the change of CDAI at week 16 and week 52 will also be evaluated. The cytokine revealed a significant relationship with clinical improvement will be selected. Multivariable linear regression models will be used to confirm the association of selected cytokines and demographics with clinical improvement. The cytokines which show strongest predictive value in multivariate analyses will be used in ROC analysis. ROC of selected cytokine will be generated to find optimal cut-off of cytokine level as predictor for clinical improvement. The predictive power of cytokine will be examined by calculating the area under the ROC curve.

Software Used:

STATA

Project Timeline:

Date to start project: MARCH 2021
Date to complete analysis: MARCH 2020 - APRIL 2021
Date to Draft manuscript: MAY 2021 - JUN 2021
Date to Submit Manuscript: JUN 2021

Dissemination Plan:

Results from the study may be communicated to target audiences through posters, abstracts, and presentations. Besides, a manuscript will be completed and submitted for publication in a relevant peer-reviewed journal. The investigators will acknowledge use of data from the YODA Project on all study products, which will be shared at the time of submission.

Bibliography:

1. Peyrin-Biroulet, L., et al., Efficacy and safety of tumor necrosis factor antagonists in Crohn's disease: meta-analysis of placebo-controlled trials. Clin Gastroenterol Hepatol, 2008. 6(6): p. 644-53.
2. Roda, G., et al., Loss of Response to Anti-TNFs: Definition, Epidemiology, and Management. Clin Transl Gastroenterol, 2016. 7: p. e135.
3. Sandborn, W.J., et al., Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med, 2013. 369(8): p. 711-21.
4. Feagan, B.G., et al., Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. N Engl J Med, 2016. 375(20): p. 1946-1960.
5. Monin, L., et al., Ustekinumab in bio-naive and bio-failure Crohn's disease patients: Results from a << real-life >> monocentric cohort. Dig Liver Dis, 2020.
6. Singh, S., et al., Primary Non-Response to Tumor Necrosis Factor Antagonists is Associated with Inferior Response to Second-line Biologics in Patients with Inflammatory Bowel Diseases: A Systematic Review and Meta-analysis. J Crohns Colitis, 2018. 12(6): p. 635-643.
7. Gole, B. and U. Potocnik, Pre-Treatment Biomarkers of Anti-Tumour Necrosis Factor Therapy Response in Crohn's Disease-A Systematic Review and Gene Ontology Analysis. Cells, 2019. 8(6).
8. Linares-Pineda, T.M., et al., Pharmacogenetic biomarkers of response in Crohn's disease. Pharmacogenomics J, 2018. 18(1): p. 1-13.

Supplementary Material:

https://yoda.yale.edu/sites/default/files/serum_cytokines_in_predicting_outcomes_to_ustekinumab_in_patients_with_crohns_disease.docx