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General Information

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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/yoda_project_coi_form_for_data_requestors_2019-larry_0.pdf

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019-tianxi_0.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. [NCT00264550 - C0524T06 - A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNF \$\alpha\$ Monoclonal Antibody, Administered Subcutaneously, in Subjects with Active Rheumatoid Arthritis Despite Methotrexate Therapy](#)

4. [NCT00361335 - C0524T12 - A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNF \$\alpha\$ Monoclonal Antibody, Administered Intravenously, in Subjects with Active Rheumatoid Arthritis Despite Methotrexate Therapy](#)
5. [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](#)
6. [NCT00269867 - C0168T22 - A Placebo-Controlled, Double-Blinded, Randomized Clinical Trial of Anti-TNF Chimeric Monoclonal Antibody \(cA2\) in Patients With Active Rheumatoid Arthritis Despite Methotrexate Treatment](#)
7. [NCT00236028 - C0168T29 - A Randomized, Double-blind, Trial of Anti-TNF \$\alpha\$ Chimeric Monoclonal Antibody \(Infliximab\) in Combination With Methotrexate Compared With Methotrexate Alone for the Treatment of Patients With Early Rheumatoid Arthritis](#)
8. [NCT01551290 - CR018769 - A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Infliximab in Chinese Subjects With Active Ulcerative Colitis](#)
9. [NCT00973479 - CNTO148ART3001 - A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, an Anti-TNF \$\alpha\$ Monoclonal Antibody, Administered Intravenously, in Patients With Active Rheumatoid Arthritis Despite Methotrexate Therapy](#)
10. [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](#)
11. [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](#)

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

Research Proposal

Project Title

Cross-Trial Comparisons of Biologic Therapies for Auto-Immune Diseases

Narrative Summary:

The incorporation of biologic therapies into clinical practice has improved the medical management of rheumatoid arthritis (RA) and inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC). When conventional treatments fail, biologic agents such as infliximab, adalimumab, or golimumab may be used. While these medications have been shown to be effective in placebo-controlled trials, there has been a lack of trials comparing agents directly. This study proposes validating a novel statistical method for the comparison of biologic therapies across trials by performing network meta-analysis utilizing a repository of existing biologic trial data.

Scientific Abstract:

Background: Biologics are used widely in patients with UC and RA but head-to-head comparisons of such therapies are lacking.

Objective: To conduct cross-trial comparisons of biologics for UC and RA using a network meta-analysis approach and to validate a novel statistical method that examines the proportion of treatment effect explained by surrogate markers.

Study Design: In comparisons of UC biologics, participants will be grouped into those in trials for infliximab vs. placebo and in trials for golimumab vs. placebo. The primary outcome will be clinical remission at week 52. The surrogate measure is clinical remission at week 8. In comparisons of RA biologics, participants will be grouped into those in trials for golimumab vs. golimumab in combination with methotrexate and trials for infliximab in combination with methotrexate vs. methotrexate. The primary outcome will be change from baseline of antinuclear antibodies (aCL) at week 54.

Participants: Adults ≥ 18 years who meet the study inclusion criteria will be included.

Main Outcome Measures: The main outcome measures include clinical response, clinical remission, and incidence of the development of aCL. Additional outcomes of interest include endoscopic healing, antibody formation, and health-related quality of life.

Statistical Analysis: Inverse probability weighted and doubly robust estimators will be obtained for the proportion of treatment effect explained by surrogates. Network meta-analysis will be performed and consistency assumptions will be checked using net heat plots and node splitting.^{1,2}

Brief Project Background and Statement of Project Significance:

Randomized controlled trials aim to identify efficacious and safe treatments to improve health and reduce the risk of negative outcomes. However, RCTs are typically long and costly, and there has been a growing interest in identifying and validating surrogate markers to infer treatment effects on outcomes.^{3,4,5} The identification and validation of appropriate surrogate markers has the potential to allow for earlier testing of treatment effects, thus reducing the cost of expensive trials, cutting the time to market for new therapies, and decreasing patient burden if the true endpoint is invasive.

We have proposed inverse-probability weighted and doubly robust estimators for the proportion of treatment effect explained by surrogate markers. To validate our statistical method, we aim to examine a data application of real-world interest – head-to-head trials of biologic therapies for patients with UC and RA. UC is a chronic inflammatory disorder of the large bowel and is characterized by bloody diarrhea, fecal urgency, and abdominal pain.⁶ When conventional treatments such as corticosteroids fail, biologic therapies such as infliximab or golimumab are often used.⁷ While these therapies have been shown to be effective in placebo-controlled RCTs, and there exist some head-to-head trials comparing biologic therapies for RA patients, there have been very few trials directly comparing biologic therapies in UC patients.⁸ One of the first such trials, a phase 3b trial of vedolizumab vs. adalimumab for patients with moderate-to-severe UC, was conducted at 245 centers in 34 countries, and showed that vedolizumab was superior to adalimumab with respect to achievement of clinical remission and endoscopic improvement, but not corticosteroid-free clinical remission.⁹ However, the researchers were unable to postulate an explanation for the inconsistency of the results between the primary and secondary remission outcomes, and conclude that this question requires further investigation. We propose to conduct a network meta-analysis to make head-to-head comparisons between biologic therapies for UC.

In summary, there is a need for more cross-trial data evaluating the efficacy of biologic treatments in UC patients, and analysis of such data with our novel statistical method and network meta-analysis methods may allow for the identification and validation of surrogate markers for important UC clinical outcomes.

Specific Aims of the Project:

- 1) We have proposed a general statistical method that allows for robust estimation of the proportion of treatment effect that can be explained by surrogate markers. To validate our method, the primary aim of this study will be to examine the proportion of treatment effect explained by clinical remission at week 8 on the outcome of interest – clinical remission at week 52 in patients with active UC. This will be assessed in cross-trial comparisons for infliximab vs. placebo and golimumab vs. placebo using network meta-analysis methods. Clinical efficacy will be assessed by rates of clinical remission as measured by a Mayo Score <2 for UC. Secondary endpoints will include clinical response, endoscopic healing, adverse events, rates of antibody formation, and health-related quality of life.
- 2) The secondary aim of this study will be to examine the proportion of treatment effect explained by the surrogate marker – anti-cardiolipin antibodies (aCL) at week 8 on the outcome of interest – aCL incidence at week 54 in RA patients.

What is the purpose of the analysis being proposed? Please select all that apply.

- Confirm or validate previously conducted research on treatment effectiveness
 - Summary-level data meta-analysis
 - Summary-level data meta-analysis using only data from YODA Project
 - Participant-level data meta-analysis
 - Participant-level data meta-analysis using only data from YODA Project
 - Develop or refine statistical methods
 - Research on comparison group
 - Research on clinical prediction or risk prediction
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Research Methods

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

The database will be queried for all clinical trial data evaluating efficacy and safety of biologic therapies in UC or RA patients. Based on a preliminary evaluation of the data available on the website, we expect to procure data related to infliximab and golimumab use. Additional drugs of interest, should they become available in the interim, would include adalimumab, vedolizumab, and/or methotrexate. All patients included in the original clinical trial data will be included in this sub-analysis.

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

The primary outcome evaluated will be clinical remission at week 52. Clinical remission will be defined as a Mayo Score less than 2 and no subscore > 1 on any of the four subcomponents for UC.

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

The main predictor variable will be the binary surrogate marker, i.e. clinical remission at week 8.

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

Additional variables of interest will include clinical response, endoscopic healing, adverse events, antibody formation, and health-related quality of life. Confounders of interest, such as patient demographic data (age, sex, ethnicity) will be used to control for baseline differences. Clinical response will be defined as a decrease in the Mayo score by 2 (with all subscores less than or equal to 1) in UC. Endoscopic activity will be defined as mucosal healing: a Mayo endoscopic subscore of 0 or 1 for UC. Antibody formation will be assessed by trough drug level and detectable antibodies. Finally, health-related quality of life will be assessed with the SIBD-Q score.

Statistical Analysis Plan:

Comparison of continuous variables will be performed by t tests or Mann-Whitney test, as appropriate. Comparison of categorical variables will be performed by Chi square tests or Fisher Exact tests, as appropriate. Our proposed inverse-probability weighted and doubly robust estimators will be used to estimate the proportion of treatment effect explained by surrogate markers on the outcome. Network meta-analysis methods will be used to make cross-trial comparisons of infliximab vs. golimumab despite no clinical trials directly comparing the two drugs for UC patient outcomes.

Software Used:

RStudio

Project Timeline:

Anticipated Project Start Date (data access granted): March 1, 2019

Analysis Completion Date: May 1, 2019

Report of Results to YODA: June 1, 2019

Date of First Manuscript Draft: June 15, 2019

Date of Manuscript Submission: July 15, 2019

Dissemination Plan:

The expected audience for this work includes biostatisticians who are interested in the development and application of our novel statistical method, as well as practicing general gastroenterologists, IBD sub-specialists, and rheumatoid arthritis specialists. Potential journals for submission include *Biometrika*, *Biometrics*, and *Statistics in Medicine*.

Bibliography:

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