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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: CT DPH through Yale Emerging Infections Program; Yale PhD Student funds
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_kc_signed.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_dmw_signed.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. NCT00264537 - C0524T05 - A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNFa Monoclonal Antibody, Administered Subcutaneously, in

Methotrexate-naïve Subjects with Active Rheumatoid Arthritis
4. NCT00264550 - C0524T06 - A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNFa Monoclonal Antibody, Administered Subcutaneously, in Subjects with Active Rheumatoid Arthritis Despite Methotrexate Therapy
5. NCT00265083 - C0524T09 - A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNFa Monoclonal Antibody, Administered Subcutaneously, in Subjects with Active Ankylosing Spondylitis
6. NCT00299546 - C0524T11 - A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNFa Monoclonal Antibody, Administered Subcutaneously in Subjects with Active Rheumatoid Arthritis and Previously Treated with Biologic Anti TNFa Agent(s)
7. NCT00361335 - C0524T12 - A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNFa Monoclonal Antibody, Administered Intravenously, in Subjects with Active Rheumatoid Arthritis Despite Methotrexate Therapy
8. 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
9. NCT01248780 - C0524T28 - A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of Golimumab in the Treatment of Chinese Subjects with Active Rheumatoid Arthritis Despite Methotrexate Therapy
10. NCT01248793 - C0524T29 - A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of Golimumab in the Treatment of Chinese Subjects with Ankylosing Spondylitis
11. NCT00207662 - C0168T21 - ACCENT I - A Randomized, Double-blind, Placebo-controlled Trial of Anti-TNFa Chimeric Monoclonal Antibody (Infliximab, Remicade) in the Long-term Treatment of Patients With Moderately to Severely Active Crohn's Disease
12. NCT00207766 - C0168T26 - ACCENT II - A Randomized, Double-blind, Placebo-controlled Trial of Anti-TNF Chimeric Monoclonal Antibody (Infliximab, Remicade) in the Long Term Treatment of Patients With Fistulizing CROHN'S Disease
13. NCT00004941 - C0168T20 - A Placebo-controlled, Repeated-dose Study of Anti-TNF Chimeric Monoclonal Antibody (cA2) in the Treatment of Patients with Enterocutaneous Fistulae as a Complication of Crohn’s Disease
14. 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
15. NCT00265096 - C0524T08 - A Multicenter, Randomized, Double-blind, Placebo controlled Trial of Golimumab, a Fully Human Anti-TNFa Monoclonal Antibody, Administered Subcutaneously in Subjects with Active Psoriatic Arthritis
16. NCT01551290 - CR018769; REMICADEUCO3001 - A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Infliximab in Chinese Subjects With Active Ulcerative Colitis
17. NCT01190839 - REMICADECRD3001 - Prospective, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial Comparing REMICADE (Infliximab) and Placebo in the Prevention of Recurrence in Crohn's Disease Patients Undergoing Surgical Resection Who Are at Increased Risk of Recurrence
18. NCT00269854 - C0168T16 - A Placebo-Controlled, Dose-Ranging Study Followed by a Placebo-Controlled, Repeated-Dose Extension of Anti-TNF Chimeric Monoclonal Antibody (cA2) in the Treatment of Patients With Active Crohn's Disease
19. NCT00973479 - CNTO148ART3001 - A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, an Anti-TNFalpha Monoclonal Antibody, Administered Intravenously, in Patients With Active Rheumatoid Arthritis Despite Methotrexate Therapy
20. 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
21. NCT00207714 - C0524T02 - A Randomized, Double-blind, Dose-ranging Trial of CNTO 148 Subcutaneous Injection Compared With Placebo in Subjects With Active Rheumatoid Arthritis Despite Treatment With Methotrexate
22. 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
23. NCT02186873 - CNTO148AKS3001 - A Study of Golimumab in Participants With Active Ankylosing

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Spondylitis
24. NCT02181673 - CNTO148PSA3001 - A Study of Golimumab in Participants With Active Psoriatic Arthritis
25. NCT01863771 - CNTO148UCO3001 - A Safety and Effectiveness Study of Golimumab in Japanese Patients 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

Estimating the association between TNF inhibitors and Legionnaires' disease and Listeriosis: A Meta-analysis

Narrative Summary:

Tumor Necrosis Factor Inhibitors (TNFi) are commonly prescribed for auto-immune diseases, but they can also place individuals at increased risk for severe infections. There is an FDA warning stating that TNFi could be associated with an increased risk of Legionnaires' disease and Listeriosis. These studies could not clarify if the increased risk was due to TNFi use or the underlying autoimmune disease. This is optimally answered through an individual patient-level meta-analysis of TNFi clinical trials. These results can be used to make more targeted risk assessments when prescribing TNFI and also inform epidemiological understanding of Legionnaires' disease and Listeriosis incidence.

Scientific Abstract:

Background: Tumor Necrosis Factor Inhibitors (TNFis) have been associated with Legionnaires' disease and Listeriosis in adverse event reporting and short-term cohort analyses. These studies are limited and are unable to distinguish between risk due to the severity of the underlying illness and risk due to TNFi.
Objective: We will use randomized control trial data for two TNFi (infliximab and golimumab) to compare the risk of Legionnaires' disease and Listeriosis among those randomized to TNFi compared to those randomized to placebo.
Study Design: An individual patient-level meta-analysis will provide estimates of pooled odds ratio (OR) and sub-group analyses to identify high risk groups and biologic mediation by sex.
Participants: Only adult participants enrolled in infliximab and golimumab RCTs available through YODA will be included in this analysis. Underlying diseases of interest include rheumatoid arthritis, ankylosing spondylitis, ulcerative colitis, Crohn's disease, and psoriasis. Only RCTs where patients were randomized to TNFi or placebo will be included in this analysis.
Main Outcome: The main outcome is a summary odds ratio estimate for the odds of Legionnaires' disease (or Listeriosis) among participants randomized to TNFi compared to those randomized to placebo.
Statistical Analysis: Study-specific odds of Legionnaires' disease and Listeriosis among those in treatment groups compared to placebo controls will be calculated. Then pooled odds ratio estimates and 95% confidence intervals will be estimated through random effects models.

Brief Project Background and Statement of Project Significance:

Certain medications can also weaken an immune system's response to infection. Tumor necrosis factor inhibitors (TNFi) are prescribed for certain autoimmune conditions (e.g. rheumatoid arthritis, ulcerative colitis, Crohn's disease) and are an alternative to conventional disease modifying anti-rheumatic drugs (cDMARDs) like methotrexate. Licensure and use of TNFis has increased since 2000 to include a broader approval range and more generics. TNFi and TNF deficiencies have been associated with inability to control both Legionella and Listeria infections in multiple murine models(1–4).

In 2011, the FDA issued a Boxed Warning for TNFi, listing Legionnaires' disease and Listeriosis as a potential adverse events (1,5,6). Legionnaires' disease (LD) is a severe bacterial pneumonia caused by Legionella spp. with a case-fatality rate around 10%. Incidence of LD in the U.S. increased steadily since 2006, reaching almost 2.5 cases/100,000 population. Listeriosis is a rare gastrointestinal infection caused by Listeria monocytogenes,

amounting to 1,600 confirmed infections per year in the US. Infections are usually linked to outbreaks and case fatality rates can be high (20%), particularly among high risk groups like the elderly, immunocompromised and pregnant women(7).

Two cohort studies conducted in France and Spain have identified an association between Legionnaires' disease and TNFi, where patients with RA taking TNFi had a higher incidence of LD compared to the general French population comparison group (8,9). A similarly- designed cohort study in Spain found that incidence of Listeriosis was higher among RA patients on TNFi compared to the general European population (10). Unfortunately, the comparison group used in these previous studies (general population) does not provide insight into whether the increased risk is due to the TNFi or the underlying condition that led to the TNFi prescription.

RCT data offers the unique ability to compare TNFi treatment to placebo and the randomization process can efficiently address confounding related to underlying disease status. Through meta-analysis, we will examine if there is evidence for an association between TNFi and Legionnaires' disease and Listeriosis. How this association may differ by sex, length of RCT follow-up and by alternative, broader disease outcomes (respiratory and gastrointestinal) will also be explored in secondary analyses. A search of available adverse outcome reports for infliximab and golimumab placebo control trials on clinicaltrials.gov revealed that Legionella pneumonia is a reported outcome among treatment groups and that pneumonia and gastrointestinal infections are frequently reported even among small RCTs.
The results of this meta-analysis will inform understanding of Legionnaires' disease and Listeriosis incidence and provide insight on understudied immune-mediated risk factors for LD and Listeriosis. This study will also provide the necessary preliminary data to launch a Danish national healthcare registry study to explore the exact nature of the association between TNFi and Legionnaires' disease and Listeriosis during the study period of 2000 to 2020.

Specific Aims of the Project:

The specific aim of this project is to estimate the association between TNFi and Legionnaires' disease (and Listeriosis). Our specific hypothesis is that TNFi are associated with an increased risk of Legionnaires' disease and Listeriosis and that this risk is not attributed to the underlying disease. In order to best address this, placebo-controlled trials will be used so that all patients have (assumed) similar underlying illness severity but are randomized to treatment.

What is the purpose of the analysis being proposed? Please select all that apply.
Preliminary research to be used as part of a grant proposal
Participant-level data meta-analysis
Participant-level data meta-analysis using only data from YODA Project

Research Methods

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

Inclusion:
All RCTs for infliximab and golimumab where patients enrolled were restricted to ages 18 and older. Only trials where placebo controls were used will be included. This includes trials for the following underlying conditions: rheumatoid arthritis, ulcerative colitis, Crohn's disease, ankylosing spondylitis, and psoriasis. Included are trials where enrollment is "despite methotrexate treatment".

Exclusion:
Trials with standard of care controls or non-methotrexate combination therapies will be excluded. All trials among patients with juvenile arthritis or asthma will be excluded.

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

The main outcome is an adverse event code for Legionnaires' disease or Listeriosis. These will be categorized as a binary outcome variable for our analysis.

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

The main independent variable would be treatment status. Patients randomized to TNFi (infliximab or golimumab) would be compared to the patients randomized to placebo. Patients recieving any dosage of TNFi will be grouped together.

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

Subgroup analyses:
Subgroup analysis where patients will be analyzed by sex and active ingredient (golimumab only and infliximab only analyses) will be explored. If statistical power allows, analysis by underlying condition of interest be explored. Specifically, we will examine the association among only patients with RA (n ~ 4300) and ulcerative colitis (n ~ 3700). Additionally, sensitivity analysis will be performed where combination treatment trials ("despite methotrexate trials") will be excluded.

Secondary outcomes:
Because Legionnaires' disease and Listeriosis are relatively rare diseases, we believe it's possible that very few cases may be identified as adverse events during case follow-up. Due to underdiagnosis of Legionnaires' disease and Listeriosis we also suspect that some cases may be coded as bacterial pneumonia or gastrointestinal illness. Secondary outcomes: bacterial pneumonia (regardless of cause), shigellosis, and gastro-intestinal infections. We would also like to consider a control outcome that we don't expect to differ between the two groups, such as fracture (which has been recorded as an adverse outcome in TNFi trials on clinicaltrials.gov).

Statistical Analysis Plan:

The primary statistical analysis will be a meta-analysis to estimate the pooled odds ratios and 95% confidence interval through random and/or fixed effects models. We will first estimate trial specific odds ratios (or relative risks) with corresponding 95% CIs. Then pooled effect estimates and corresponding 95%CIs will be estimated through meta-analysis models using the R packages 'meta' and/or 'metafor'. The choice between fixed or random effects models will depend on the level of between-study heterogeneity. In meta-analyses of rare events, fixed effects models are usually preferred over random effects since estimates of between study heterogeneity may not be accurate for rare events. Since we expect Legionnaires' disease and Listeriosis to be a rare event, we anticipate using fixed effects models. To summarize the effect estimates and properly assign weights to each trial included in the analysis, the Peto method will be used. This method assumes an OR close to 1 and is better for rare outcomes in studies where arms are equivalent in size (expected in RCTs)12. We will have to reassess where the ORs lie but it is expected that they will not be much greater than 1, particularly for the secondary outcomes that are more composite, such as unspecified pneumonia and gastrointestinal infections. When no events are reported in one or both study arms, a continuity correction of 0.5 will assumed in each cell.

If outcomes are not rare (as is likely with the bacterial pneumonia and gastrointestinal infection secondary outcomes), we will use fixed (Mantel-Haenszel) or random effects (DerSimonian and Laird) models with inverse variance methods. We will calculate the I2 statistic in order to assess study heterogeneity in a manner comparable to other meta-analysis of RCT adverse events. An I2 less than 25% would indicate strong heterogeneity between RCTs and the need for a random effects model.

Forest plots of effect estimates and corresponding 95% confidence intervals along with pooled estimates will be presented as the results.

If the data allows, sub-group level pooled ORs by sex will also be estimated. Some diseases like RA are more prevalent among women but the outcome of Legionnaires' disease is more prevalent among males so we would like to explore biologic modification by sex. Golimumab-only and infliximab-only sub-group analysis will also be conducted to understand if any TNFi and disease association is actually driven by a specific active ingredient.
Software Used:
RStudio
Project Timeline:

This project will last approximately 1 year from data-acquisition to manuscript submission. The first month will be allocated to data cleaning and preparation, months 2-6 will be dedicated to statistical analysis, and, finally, months 6-12 will be dedicated to manuscript drafting, revisions among authors, and submission(s). Expected analysis start date is August 1, 2020, analysis completion date is January 1, 2021, manuscript first draft date is March 1, 2021,

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and first manuscript submission date/date results reported to YODA is May 1, 2021.

Dissemination Plan:

The intended product of this analysis is a high-quality manuscript to be submitted to peer-reviewed journals such as Clinical Infectious Diseases, Journal of the American Medical Association, Rheumatology, and American Journal of Epidemiology. The target audience are public health officials interested in understanding Legionnaires' disease and Listeriosis infectious disease trends, and clinicians such as rheumatologists who may have prescribing concerns.

Bibliography:

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Supplementary Material:

https://yoda.yale.edu/sites/default/files/yoda_datareq_update1.docx