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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?: Other

Conflict of Interest

https://yoda.yale.edu/system/files/ward_coi_updated.pdf
https://yoda.yale.edu/system/files/yoda_coi_rw_updated.pdf
https://yoda.yale.edu/system/files/yoda_coi_dasgupta_v3.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. 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
2. 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
   3. NCT00202865 - P04352 - Evaluation of Low Dose Infliximab in Ankylosing Spondylitis (CANDLE)
   4. NCT00207701 - C0168T51 - A Randomized, Double-blind Trial of the Efficacy of REMICADE (Infliximab) Compared With Placebo in Subjects With Ankylosing Spondylitis Receiving Standard Anti-inflammatory Drug Therapy
   5. NCT02186873 - CNTO148AKS3001 - A Study of Golimumab in Participants With Active Ankylosing Spondylitis
   6. NCT01453725 - P07642 - A Multicenter, Randomized, Double-blind, Placebo-controlled Study of the Effect of Golimumab Administered Subcutaneously in Subjects With Active Axial Spondyloarthritis (Also Known as MK-8259-006-02)

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

Research Proposal

Project Title

Predicting Treatment Response to Tumor Necrosis Factor Inhibitors in patients with ankylosing spondylitis

Narrative Summary:

Tumor Necrosis Factor inhibitors (TNFi) are the second line treatment for patients with active ankylosing spondylitis (AS). In randomized control trials, only half of the patients achieved a major response or clinical remission. In clinical practice, patients and providers are interested to know, how likely a patient will achieve a major response to TNFi when initiating the therapy. So the goal of this study is to investigate clinical features that predict favorable response to TNFi therapy, and to provide a probability of having a major response in individual patients.

Scientific Abstract:

Background: Tumor Necrosis Factor inhibitors (TNFi) are second line treatments for patients with active ankylosing spondylitis (AS). In randomized controlled trials (RCT), less than one-half of patients achieved a major response or clinical remission. The clinical features that may predict a favorable response to TNFi in patients with active AS is not known.
Objective: To identify clinical features that predict a favorable response to TNFi in patients with active AS, in the form of a probability score.
Study Design: This is an ad hoc study of RCTs of TNFi in patients with AS. We will request individual patient data (IPD) from trial sponsors and/or principal investigators, and aggregate all available IPD for statistical analysis.
Participants: Patients who fulfill modified New York criteria for AS, and enrolled in a double blinded RCT with at least one arm that assessed the efficacy of TNFi, at 12 weeks and 24 weeks, including adalimumab, certolizumab, etanercept, golimumab, infliximab, and biosimilar TNFi.
Main Outcome Measures: Ankylosing Spondylitis Disease Activity Score (ASDAS) major response (improvement > 2.0) vs. clinically important response (change between 1.1 – 2.0) vs. no response (change <1.1) at 24 weeks. Secondary outcomes will include Assessment in AS (ASAS) partial remission and ASAS40 responses.
Statistical Analysis: We will categorize each patient into three ASDAS response groups based on their responses at 24 weeks, and perform classification tree analysis to predict the probability of having a major response in individual patients.

Brief Project Background and Statement of Project Significance:

Tumor Necrosis Factor inhibitors (TNFi) have been widely used as the second line treatment for patients with active ankylosing spondylitis (AS) despite treatment with non-steroidal anti-inflammatory drugs. In our previous systematic review of randomized control trials of TNFi in patients with AS, about half of the participants (39.% to 58.9%) achieved ASAS40 at week 24, an indicator of major response. It remains unclear what clinical features will predict a favorable response to TNFi. In clinical practice, both patients and clinicians are interested to know, how likely an

individual patient will achieve remission after initiating TNFi therapy. The goal of our study is to investigate the predictive value of baseline clinical features for achieving a major response in the form of probability score that can be used directly in clinical practice.

Specific Aims of the Project:

Aim 1. To investigate the predictive value of baseline clinical features for achieving a major response at week 24.
Aim 2. To investigate the predictive value of baseline clinical features for achieving a major response at week 12.

What is the purpose of the analysis being proposed? Please select all that apply.
Participant-level data meta-analysis
Participant-level data meta-analysis pooling data from YODA Project with other additional data sources
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:

Data Source:
Data from double-blinded, randomized trials in patients with active ankylosing spondylitis with at least one arm assessing TNFi efficacy at week 12 and/or week 24.

Inclusion/Exclusion Criteria:
Inclusion criteria:
• Patients with ankylosing spondylitis by modified New York Criteria
• Age ? 18
• Received one of TNFi originator or biosimilar in a randomized, double-blind trial, that is registered at clinicaltrial.gov and have published trial results.
Exclusion criteria:
• Patients with non-radiographic axial spondyloarthritis

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

Patients who achieved major response, defined as change of Ankylosing Spondylitis Disease Activity Score (ASDAS) more than 2.0
vs. who achieved clinically important response, defined as change of ASDAS 1.1 – 2.0
vs. who had no response, defined as change of ASDAS less than 1.1 at 24 weeks

Alternatively, we will use: a) ankylosing spondylitis assessment 40% (ASAS40) as an indicator for major response, ASAS20 as an indicator for clinically important response, and not achieving ASAS40 or ASAS20 as no response;
b) presence or absence of partial remission at 12 or 24 weeks.

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

• Demographics: Age, Sex, smoking (current, past, never), Body Mass Index
• SpA related features: Disease Duration, Spondyloarthritis-associated diagnoses
• Labs: HLA-B27 status, CRP, ESR
• Concomitant therapy

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

Complete List of Variables
• Demographics: Age, Sex, ethnicity, country of origin,
• Co-existing conditions: smoking, BMI, co-morbidities (eg osteoporosis, heart disease)
• Spondyloarthritis- related features: Disease Duration, Back pain duration, SpA associated diagnoses, total hip arthroplasty
• Labs and disease activity scores: HLA-B27 status, baseline Bath AS Disease Activity Index (BASDAI) (in

individual scores), Bath AS Functional Index (BASFI) (in individual scores), patient global assessment, CRP, ESR
• X ray reading
• Concomitant therapy
• Prior exposure/response to TNFi

Statistical Analysis Plan:

We will use descriptive analysis to summarize the data.
We will group the participants into major response vs. clinically important response vs. no response based on the change of ASDAS at week 24, and perform classification tree analysis using the variables listed in the Main Predictor/independent variable section to identify predictors for a major response at week 24. A similar analysis will be performed for response at week 12. We plan to perform a sensitivity analysis using ASAS40, ASAS20 as indicator for major response and clinically important response, and for partial remission.
Software Used:
R

Project Timeline:

Anticipated project start date: 07/01/2019
Analysis completion date: 12/31/2019
Manuscript Draft: 01/2020
Manuscript Submission: spring 2020
Results report back to YODA: 2020

Dissemination Plan:

Manuscript(s) published in a peer-reviewed journal. Target audience are practicing rheumatologists and clinical researchers. Potential suitable journals include Arthritis Rheumatology, Annals of Rheumatic Diseases, and Journal of Rheumatology.

Bibliography:

1. Wang R, Dasgupta A, Ward MM. Comparative Efficacy of Tumor Necrosis Factor-? Inhibitors in Ankylosing Spondylitis: A Systematic Review and Bayesian Network Metaanalysis. J Rheumatol. 2018 Jan 15;
2. Inman RD, Davis JC, Heijde DVD, Diekman L, Sieper J, Kim SI, et al. Efficacy and safety of golimumab in patients with ankylosing spondylitis: Results of a randomized, double-blind, placebo-controlled, phase III trial. Arthritis Rheum. 2008 Nov;58(11):3402–12.
3. van der Heijde D, Dijkmans B, Geusens P, Sieper J, DeWoody K, Williamson P, et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis: Results of a randomized, placebo-controlled trial (ASSERT). Arthritis Rheum. 2005 Feb;52(2):582–91.
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5. Bao C, Huang F, Khan MA, Fei K, Wu Z, Han C, et al. Safety and efficacy of golimumab in Chinese patients with active ankylosing spondylitis: 1-year results of a multicentre, randomized, double-blind, placebo-controlled phase III trial. Rheumatology. 2014 Sep 1;53(9):1654–63.