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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

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

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

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)

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

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

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

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

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

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

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

NCT02186873 - CNTO148AKS3001 - A Study of Golimumab in Participants With Active Ankylosing Spondylitis

NCT02181673 - CNTO148PSA3001 - A Study of Golimumab in Participants With Active Psoriatic Arthritis

NCT01004432 - CNTO148ART3002 - Golimumab in Rheumatoid Arthritis Participants With an Inadequate Response to Etanercept (ENBREL) or Adalimumab (HUMIRA)

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)

NCT00975130 - P06129 - An Open-Label Study Assessing the Addition of Subcutaneous Golimumab (GLM) to Conventional Disease-Modifying Antirheumatic Drug (DMARD) Therapy in Biologic-Naïve Subjects With Rheumatoid Arthritis (Part 1), Followed by a Randomized Study Assessing the Value of Combined Intravenous and Subcutaneous GLM Administration Aimed at Inducing and Maintaining Remission

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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_ahmad_abuhelwa_0.pdf
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https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_michael_wiese_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

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

Research Proposal

Project Title

Predictors of therapeutic and adverse effect outcomes of golimumab

Narrative Summary:

There have been several important developments in the treatment of autoimmune diseases over the last decade, including the introduction of golimumab. However, response and toxicity to golimumab can be unpredictable. For example, ~ 40% of the eligible patients who initiate golimumab therapy for rheumatoid arthritis do not respond, while 60% experience some form of toxicity. Thus, more research is required to confirm and explore novel predictive markers of therapeutic and adverse effects of golimumab in the treatment of autoimmune diseases (e.g. rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis).

Scientific Abstract:

Background: Golimumab is an important treatment option for various autoimmune diseases. However, response and toxicity to golimumab can be unpredictable with ~ 40% of patients not responding or experiencing toxicity.
Objectives: To develop predictive models of therapeutic and adverse effect outcomes in patients using golimumab to treat various autoimmune diseases. Being able to identify the profile of expected therapeutic and adverse effect outcomes may enable patients and clinicians to make better decisions regarding whether to commence, continue, discontinue or change dosing of golimumab.
Study design: Pooled analysis of individual participant data from studies investigating golimumab, and relevant comparator arms for the treatment of patients with rheumatoid arthritis (RA), psoriatic arthritis (PA), ankylosing spondylitis (AS) and ulcerative colitis (UC)
Participants: Patients with RA, PA, AS, or UC treated with golimumab or relevant comparator arms
Main outcome measure(s): Measures of therapeutic (e.g. remission, response, quality of life and survival) and adverse effect outcomes in accordance with the respective diseases and / or medications
Statistics: Cox-proportional hazard/time-to-event models will be used to assess the association between potential predictors and the time to an adverse effect or response/progression/survival. The association of potential predictors with binary outcomes will be modelled using logistic regression. Longitudinal analysis will be used to assess the patterns of longitudinal changes of key continuous variables

Brief Project Background and Statement of Project Significance:

Golimumab is a Tumour Necrosis Factor inhibitor that belongs to a class of medicines called biological disease modifying antirheumatic drugs (bDMARDs). Biological DMARDs, including golimumab, are now very commonly used by patients with RA, PA, AS, and UC and are expensive. Unfortunately, the effect of golimumab takes weeks to months to become apparent and in patients who do not respond (~40%), value time has been lost which leads to increased morbidity and mortality [1-4]. Further, golimumab is associated with potentially life-threatening toxicities. Therefore, more research is required to confirm and explore novel predictive markers of therapeutic and adverse effects of golimumab to ultimately help clinicians make informed decisions regarding the use of golimumab to treat autoimmune diseases.
In this project, clinical prediction models of therapeutic and adverse effects outcomes to golimumab and relevant comparator medicines (e.g. methotrexate in RA patients) will be developed from available data from RA, PS, AS, and UC. The analysis will identify and validate predictors of the most important adverse effects, and clinical/biological/patient predictors of therapeutic outcomes such as response/progression, quality of life and survival.
Ultimately developing clinical prediction models for golimumab in patients with autoimmune diseases could be used to make informed decisions as to whether to commence, continue, discontinue or change dosing of golimumab which can eventually lead to improved health outcomes and significant cost savings.

Specific Aims of the Project:

Specific hypothesis
The hypothesis of this project is that clinical prediction models of therapeutic and adverse effects outcomes of golimumab and relevant comparator medicines can be developed from available clinical trial data to enable informed-decisions to be made regarding golimumab therapy in patients with autoimmune diseases.
Specific aims
1. Identify baseline and on-treatment predictors and develop clinical prediction models of the key adverse effects of golimumab and relevant comparator medicines when used in the treatment of autoimmune diseases (RA, PA, AS, and UC).
2. Identify baseline and on-treatment predictors and develop clinical prediction models of the key therapeutic outcomes (response / progression, quality of life and survival) of golimumab and relevant comparator medicines when used in the treatment of autoimmune diseases.
3. Evaluate the heterogeneity of treatment (golimumab versus relevant comparator medicines (e.g methotrexate in RA patients) adverse effects and therapeutic outcomes according to model predicted risk.
4. Identify baseline and on-treatment predictors and develop clinical prediction models of patient exposure to golimumab and relevant comparator medicines.

What is the purpose of the analysis being proposed? Please select all that apply.
New research question to examine treatment safety
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
Research on comparison group
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:

To precisely and validly determine the relationship between potential predictors and outcomes of interest it is important to have the maximum sample size possible across a range of different study populations (an increased number of studies increases the population diversity and is thus more comparable to standard clinical practice). Therefore, all studies collecting baseline and follow-up clinical characteristic data, as well as adverse event or therapeutic outcome data for patients treated with golimumab and relevant comparator medicines for the treatment of RA, PS, AS, and UC have been selected (model building will use the per-protocol populations). Particular care has been taken to select studies that assess the target populations for golimumab (i.e. RA, PS, AS, and UC), rather than just every study that has examined golimumab. Data from the comparator arms will be required to understand the heterogeneity in treatment effect according to identified risk factors (analyses of the heterogeneity of treatment effects will use the intent-to-treat populations), and whether the risk factors identified are specific to golimumab or are common across multiple therapies.

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

Outcomes including response/progression/clinical remission (e.g. American College of Rheumatology Response Criteria (e.g.20/50/70), EULAR response classification, DAS28 scores, Psoriasis Area and Severity Index (PASI), Assessment in Spondyloarthritis International Society (ASAS) classification criteria (e.g. ASAS 20), change from baseline in the Bath Ankylosing Spondylitis Functional Index (BASFI), Simplified Disease Activity Index, Clinical Disease Activity Index Modified Total Sharp Score, quality of life changes (e.g. Health Assessment Questionnaire-Disability Index, Rheumatoid Arthritis Quality of Life questionnaire), treatment satisfaction questionnaire, pain, fatigue, survival, adverse event outcomes (clinician/patient reported adverse effects defined by grade and sentinel events [e.g. hospitalization/discontinuation]), and drug exposure (concentration). Where a metric is derived, the data required to calculate the score will be required (e.g. 28 Tender Joint Count, 28 Swollen Joint Count, Patient Global assessment of disease activity, Physician global assessment of disease activity, pain score, ESR and CRP). The most recent in scope data cuts of these variables are required.

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

Most data collected within trial contains some information on the immune system, disease severity, prognosis, toxicity risk or drug exposure. Thus, it's important to access all the baseline/pre-treatment and follow-up clinical/biological/patient characteristic data collected on an individual for any given study. Covariates to be explored include, but not limited to
• Characteristic data – e.g. age, sex, race/ethnicity, BMI, weight, disease duration prior to therapy initiation, smoking Hx, alcohol Hx, family Hx of disorders, and measures of performance/QOL/PRO
• Lab data: e.g. levels of ALB, BILI, full blood count (e.g. HGB, RBC, MCV, WBC, lymphocyte, neutrophil, monocyte, platelets), INR, blood glucose, HBA1C, creatinine, CRP, ESR, calcium, total protein, cholesterol (LDL, HDL, total TG), RF titre, anti-CCP titre and blood urea nitrogen
• Disease classification/common biomarker data, e.g. prior therapy, prior surgery, time to response / progression for previous therapies, time since diagnosis, number and sites of tender and swollen joints, line of therapy, joint space, pathological features of T-cells, shared epitope status, and disease / drug specific genotype data.

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

• Other common predictors, e.g. concomitant medications (including use of rescue medicines such as corticosteroids), respiratory comorbidity (e.g. asthma), comorbid diseases (e.g. peripheral vascular disease, cerebrovascular disease, diabetes, Hepatitis C infection), simplified comorbidity score, organ dysfunction (e.g. liver, lung or renal), and other clinical, biological, vital statistics, laboratory, imaging, pharmacokinetic and patient-reported outcomes measures that are commonly collected in clinical trials and related to therapeutic and adverse outcomes.

• Post-baseline values. Post-baseline values (including longitudinal relationships/patterns) can be useful early markers of therapeutic outcomes or adverse events. Variables include time-varying clinical (including adverse events such as immune related adverse events and comorbidities), radiological (e.g. joint space narrowing, erosions), biological/laboratory (e.g. haemoglobin, red cell count, WBC, Liver function tests, drug exposure/concentration), vital statistics (e.g. weight, heart rate, blood pressure), disease classification, patient-reported outcomes, and other common time-dependent predictor data.

Statistical Analysis Plan:

Cox-proportional hazard / time-to-event models will be used to assess the association between potential predictors and the time to an adverse effect or response / progression / survival. Associations will be reported primarily as hazard ratios with 95% confidence intervals. The association of potential predictors with binary outcomes (e.g. yes / no) will be modelled using logistic regression and will be reported as odds ratios with 95% confidence intervals. Longitudinal analysis (e.g. linear and non-linear mixed effect modelling) will be used to assess the nature and patterns of longitudinal changes of key continuous variables (e.g. drug concentration, immune cell counts, number of swollen and tender joints).
The R Software and packages will be used for data preparation, modelling and graphical output. Non-linear mixed effect modelling of concentration and disease activity measures will be evaluated using the “R” Software (R Core Team) with Rtools (an Rtoolset), and the R packages ‘RxODE’, ‘nlmixr’, ‘pmetrics’ and ‘mrgsolve’. NONMEM will be used if available.
Potential predictors will be prioritised according to biological/clinical plausibility and prior evidence of association with the relevant outcome (adverse events, therapeutic response, drug exposure). Should multiple values of a covariate be recorded multiple times for a single visit (e.g. blood pressure) the mean of the multiple reads taken at each visit will be used. Crude associations will be reported based on univariate analysis (adjusting only for the clinical trial and where appropriate the medicines used), and adjusted associations based on a multivariable analysis. Continuous variables will be assessed for non-linear associations. Clinical prediction models will be developed using multivariable analysis. Penalisation method will be used to minimise the risk of model overfitting. Early markers of exposure, response and toxicity will be primarily evaluated using a landmark approach where possible. Landmark time will be dependent on the time points available in individual studies, and the time frame of changes in each specific predictor variable. As this analysis is primarily hypothesis generating and will require subsequent validation of any findings, no formal adjustment for multiple testing is intended. However, this limitation will be clearly stated in any publications of results. As it is expected that < 5% of data will be missing for most potential predictor variables a complete case analysis is planned. Should variables with substantial missing data be present, the pattern and likely cause of the missing data will be evaluated and if missing at random is reasonable to assume then imputation will be undertaken.
Analyses will include evaluating predictors of therapeutic and adverse outcomes for relevant comparator medicines. Analyses will also include evaluating the heterogeneity in toxicity incidence and therapeutic profiles according to modelled risk for golimumab as compared to relevant comparator arms (e.g. methotrexate). Such analyses will allow a better understanding of the benefits of golimumab, and whether the relationships identified are specific to golimumab, the comparator medicine or are common across patients.
Predictors that have a clinically meaningful (e.g. double the risk) effect on outcome and adverse effects will be of primary interest. Based upon a 30% incidence of toxicity, a sample size of approximately 180 is required to detect a predictor associated with a two-fold risk (?=0.05 with 80% power). Based upon an event rate of 40% during trial follow-up (e.g. for response), approximately 160 participants are required for 80% power to detect a predictor associated with a two-fold hazard of the event (?=0.05).

Project Timeline:

The project is expected to take 2 years from the date of data access and the research group is prepared to renegotiate access at 12 months intervals. Estimated start date 1 May 2019 with all analysis completed by 30 April 2021. Manuscripts will be drafted and submitted at each stage of the proposed project. Results will be reported back to YODA prior to manuscript acceptance

Dissemination Plan:

Results of all completed analyses will be published in peer-reviewed journals and where possible also presented at scientific meetings. Manuscript(s) will be submitted as soon as possible following completion of the requisite analyses. Suitable journals include Arthritis and Rheumatology, Arthritis Care and Research, Rheumatology, Annals of the Rheumatic Diseases, and British Journal of Clinical Pharmacology.

Bibliography:

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4. Kavanaugh, A., et al., Golimumab in psoriatic arthritis: one?year clinical efficacy, radiographic, and safety results from a phase III, randomized, placebo?controlled trial. Arthritis & Rheumatism, 2012. 64(8): p. 2504-2517.