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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

Associated Trial(s): NCT00036374 - A Randomized, Double-Blind Trial of Anti-TNF Chimeric Monoclonal Antibody (Infliximab) in Combination With Methotrexate for the Treatment of Patients With Polyarticular Juvenile Rheumatoid Arthritis
NCT00036439 - A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients With Active Ulcerative Colitis
NCT00096655 - A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients With Active Ulcerative Colitis
NCT00094458 - Multicenter, Randomized, Double-Blind, Active Controlled Trial Comparing REMICADE® (infliximab) and REMICADE plus Azathioprine to Azathioprine in the Treatment of Patients with Crohn's Disease Naive to both Immunomodulators and Biologic
NCT00336492 - A Phase 3, Randomized, Open-label, Parallel-group, Multicenter Trial to Evaluate the Safety and Efficacy of Infliximab (REMICADE) in Pediatric Subjects With Moderately to Severely Active Ulcerative Colitis
NCT00264537 - 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 - 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 - 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 - 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
NCT00361335 - 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 - 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 - 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 - 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
NCT00207662 - 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
NCT00207766 - 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
NCT00004941 - 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
NCT00269867 - A Placebo-Controlled, Double-Blinded, Randomized Clinical Trial of Anti-TNF Chimeric

Monoclonal Antibody (cA2) in Patients With Active Rheumatoid Arthritis Despite Methotrexate Treatment
NCT00236028 - A Randomized, Double-blind, Trial of Anti-TNFa Chimeric Monoclonal Antibody (Infliximab) in Combination With Methotrexate Compared With Methotrexate Alone for the Treatment of Patients With Early Rheumatoid Arthritis
NCT00202865 - Evaluation of Low Dose Infliximab in Ankylosing Spondylitis (CANDLE)
NCT00537316 - Efficacy & Safety of Infliximab Monotherapy Vs Combination Therapy Vs AZA Monotherapy in Ulcerative Colitis (Part 1) Maintenance Vs Intermittent Therapy for Maintaining Remission (Part 2)
NCT00265096 - 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
What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Impact of Biologic Therapy on the Risk of Arterial and Venous Thromboembolic Events in Chronic Autoimmune Diseases: A Post-Hoc Analysis of RCTs

Narrative Summary:
Chronic inflammation is an independent risk factor for cardiovascular diseases and venous thromboembolism (VTE), and hence, patients with autoimmune diseases, such as rheumatoid arthritis, inflammatory bowel diseases, psoriatic arthritis, and ankylosing spondylitis are at increased risk. This risk is particularly increased during disease flares or prolonged activity indicating a correlation with the inflammatory burden. The aim of this study is to evaluate the effect of biologic therapy, in particular response to treatment, on the risk of cardiovascular events and VTE, and related mortality, in randomized controlled trials (RCTs) of biologic therapy in autoimmune diseases.

Scientific Abstract:
Background: Patients with autoimmune diseases, like rheumatoid arthritis (RA), inflammatory bowel diseases (IBD), psoriatic arthritis (PsA), and ankylosing spondylitis (SpA) are at increased risk of cardiovascular events and venous thromboembolism (VTE), particularly during periods of high disease activity. It is unclear whether biologic therapy modifies this risk.
Objective: To evaluate the association between biologic therapy and risk of major adverse cardiovascular events and VTE in autoimmune diseases.
Study Design: Individual participant-level pooled analysis of RCTs
Participants: Patients in phase III RCTs of infliximab and golimumab in RA, IBD, PsA, or SpA, receiving either placebo or active agent.
Main Outcome Measures: Risk of cardiovascular events and VTE in (a) patients treated with biologics (vs. placebo), and (b) in patients with response to therapy (vs. non-responders).
Statistical Analysis: We will perform 2 separate Cox proportional hazard analyses to evaluate the association between (a) receipt of biologics (vs. placebo), and (b) response to therapy (vs. non-response) on cardiovascular and VTE risk, after pooling data from included RCTs. All analyses will be adjusted for confounders – baseline disease activity, traditional cardiovascular (age, sex, smoking, diabetes, hypertension, hyperlipidemia, obesity, personal or family history of cardiovascular disease, use of aspirin/statins) and VTE risk factors (age, sex, immobility, hospitalization, obesity, smoking, drugs), and co-interventions. Analyses will be stratified by type of autoimmune disease.

Brief Project Background and Statement of Project Significance:
Autoimmune diseases, including RA, IBD, PsA and SpA have been associated with an increased risk of cardiovascular events and venous thromboembolism.1-7 While traditional cardiovascular risk factors are not over-represented in these patients, chronic inflammation-driven accelerated atherosclerosis and prothrombotic state contribute to this increased risk.2,8 Atherosclerosis is a chronic inflammatory process in which immune cells infiltrate the arterial wall in response to chemotactic signals generated by activated endothelial cells.9,10,11 This association between autoimmune diseases and risk of cardiovascular and VTE events is particularly strong during periods of active disease as compared to periods of remission, consistent with the effect of high inflammatory burden.12,13
Few studies have investigated therapeutic strategies to reduce this risk.14-16 Aggressive treatment of autoimmune

diseases with biologic agents may conceivably decrease cardiovascular (and VTE) risk by decreasing inflammatory burden.2, 8 However, observational studies are limited in their ability to infer the effect of disease-modifying therapy on cardiovascular risk due to confounding by severity (i.e., patients with high disease activity, inherently at high cardiovascular risk, are likely to be treated with more potent biologic therapy), so the benefit of therapy may not be apparent.17 Additionally, most observational studies are also at risk of immortal-time bias.18 It is unclear whether any impact of therapy on reducing cardiovascular risk is an independent effect of the treatment or an indirect effect by reducing inflammation.
In this proposal, our objective is to study the impact of biologic therapy both directly (vs. placebo) and indirectly (by comparing responders vs. non-responders) on cardiovascular and VTE risk, within an enriched high-risk population of patients with severe active autoimmune diseases participating in well-designed clinical trials of biologic therapy. Our central hypothesis is that response to treatment (vs. non-response), and not mere receipt of biologics (vs. placebo), is associated with reduced risk of cardiovascular and VTE events in patients with autoimmune diseases. The significance of this work lies in comprehensively assessing how receipt and response to biologic therapy modifies the risk of thromboembolism in patients with autoimmune diseases, using a novel, innovative approach through post-hoc analyses of robust, late-stage clinical trials, avoiding biases of observational studies. By combining all autoimmune diseases, we anticipate sufficient number of events in trials for a well-powered analysis. From a scientific perspective, the information generated will advance understanding of atherosclerosis and thrombosis in chronic inflammatory diseases. From a clinical perspective, information generated from this study will be directly applicable to patient care offering a personalized therapeutic approach to cardiovascular risk in autoimmune diseases.

Specific Aims of the Project:
Specific aim #1: To compare risk of cardiovascular events (myocardial infarction, angina, stroke, transient ischemic attacks) and VTE in biologic vs. placebo-treated patients with autoimmune diseases, including RA, IBD, PsA and SpA, in post-hoc analysis of phase III RCTs of biologic therapy, after adjusting for baseline disease activity and traditional risk factors for cardiovascular disease and VTE.
Hypothesis: Biologic-treated patients will have marginally lower risk of cardiovascular events and VTE as compared to placebo-treated patients

Specific aim #2: To compare the risk of cardiovascular events (myocardial infarction, angina, stroke, transient ischemic attacks) and venous thromboembolism (VTE) in patients with study-defined response to therapy (regardless of intervention) against non-responders, in patients with autoimmune diseases in post-hoc analysis of phase III RCTs of biologic therapy, after adjusting for baseline disease activity and traditional cardiovascular and VTE risk factors.
Hypothesis: Patients with response to therapy (regardless of intervention) will have a significantly lower risk of cardiovascular events and VTE, as compared to patients who fail to respond to therapy.

What is the purpose of the analysis being proposed? Please select all that apply. New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:
• Trials of infliximab in rheumatoid arthritis (NCT00269867, NCT00236028)
• Trials of golimumab in rheumatoid arthritis (NCT00264537, NCT00264550, NCT00299546, NCT00361335, NCT01248780)
• Trials of infliximab in Crohn’s disease (NCT00207662, NCT00207766, NCT00004941, NCT00094458)
• Trial of infliximab in ulcerative colitis (NCT00036439, NCT00096655, NCT00336492, NCT00537316)
• Trials of golimumab in ulcerative colitis (NCT00487539)
• Trials of golimumab in psoriatic arthritis (NCT00265096)
• Trials of golimumab in ankylosing spondylitis (NCT00265083, NCT01248793)
• Trial of infliximab in ankylosing spondylitis (NCT00202865)
• Trial of infliximab in juvenile idiopathic arthritis (NCT00036374)
Inclusion criteria:
• Adults with:
o Active rheumatoid arthritis (defined as either at least 4 swollen joints and at least 4 tender joints at baseline, and meet at least 2 of the following criteria at screening and/or baseline: 1) C-reactive protein (CRP) >1.5mg/dl or erythrocyte sedimentation rate (ESR) >28 mm/hour 2) morning stiffness lasting 30 minutes or longer, 3) bone

erosion by radiography and/or magnetic resonance imaging prior to initiation of treatment with the study agent

Main Outcome Measure and how it will be categorized/defined for your study:
Main outcome measure will be cardiovascular and/or VTE events any time during the trial period
• Composite endpoint of major adverse cardiovascular events including
o Acute coronary syndrome including unstable angina, myocardial infarction,
o Ischemic heart failure
o Stroke and transient ischemic attack
o Cardiovascular mortality
• Venous thromboembolism events include
o Deep venous thrombosis
o Pulmonary embolism
o VTE-related mortality

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
• For specific aim #1, predictor would be intervention (active vs. placebo)
• For specific aim #2,
o For rheumatoid arthritis trials – Clinical response (ACR20 or 50 response defined as ?20% or 50% improvement in RA symptoms)
o For ulcerative colitis trials – Clinical response (decrease in MCS by ?3 points and 30%, with decrease in the rectal bleeding sub-score by ?1 point, or an absolute sub-score of 0 or 1)
o For Crohn's disease trials – Clinical response (decrease in CDAI by 100 [CR100] or 70 points [CR70] from baseline; reduction in number of draining fistulae by 50% from baseline, for fistulizing CD)
o For psoriatic arthritis trials – Clinical response (ACR20 response defined as improvement of >= 20% from baseline)
o For ankylosing spondylitis trials – Clinical response (AS20 response defined by the number of patients who achieved a 20% improvement and at least 1 absolute improvement on a 0 to 10 cm scale from baseline in at least 3 of the 4 domains: patient global, total back pain, function or inflammation)

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:
Key confounding variables of interest in our study are:
o Traditional cardiovascular risk factors at baseline including hypertension, hyperlipidemia/hypertriglyceridemia, obesity, diabetes mellitus, smoking status, age, sex, familial or personal history of CV disease, use of aspirin/statins
o Traditional VTE risk factors: recent major surgery, obesity, smoking, hospitalization, oral contraception, and cancer
o Biochemical measures of disease severity – baseline C-reactive protein as a categorical variable (<0.5mg/dl or ?0.5mg/dl), fecal calprotectin for IBD (<150mcg/g vs. ?150mcg/g)
o Co-interventions – concomitant use of immunomodulators like azathioprine, 6-mercaptopurine or methotrexate (yes vs. no), concomitant use of steroids and NSAIDs (yes vs. no)
o All analysis will be stratified by autoimmune disease types (RA, PsA, SpA, IBD); trials of induction and maintenance therapy will be analyzed separately

Statistical Analysis Plan:
• Impact of biologics on cardiovascular and VTE risk (vs. placebo): We will compare the baseline characteristics of biologic- vs. placebo-treated patients for key variables, and evaluate the incidence of major adverse cardiovascular events and VTE events in both groups. We will then perform multivariable Cox proportional hazard analysis after adjusting for type of autoimmune disease and relevant confounders including baseline disease activity (clinical, biochemical), traditional cardiovascular (age, sex, smoking status, diabetes, hypertension, hyperlipidemia, obesity, personal or family history of cardiovascular disease, use of aspirin/statins) and VTE risk factors (age, sex, smoking, obesity, immobility, hospitalization, procoagulant or anticoagulant) and co-interventions for autoimmune disease.
• Impact of response to therapy on cardiovascular and VTE risk (vs. non-responders): We will compare baseline characteristics of responders vs. non-responders (regardless of intervention) for key confounding variables, and evaluate the incidence of major adverse cardiovascular events and VTE events in both groups. Then we will perform multivariable Cox proportional hazard analysis after adjusting for type of autoimmune disease and relevant confounders including intervention arm, baseline disease activity, traditional cardiovascular and VTE risk factors, and co-interventions for autoimmune disease.

Analysis will be clustered by RCT, and stratified by type of autoimmune disease (RA, IBD, PsA, SpA). We will perform additional subgroup analysis by trial design (induction vs. maintenance), type of anti-TNF agent (infliximab vs. golimumab).

Project Timeline:
Once study is approved and data access provided (assuming by February 2016), our key milestones dates are:
o Project start date: March 1, 2016
o Analysis completion date: May 1, 2016
o Manuscript drafted: July 1, 2016
o Manuscript submitted for publication: August 1, 2016
o Date results reported back to YODA: August 1, 2016

Dissemination Plan:
We anticipate generation of at least 2 manuscripts from this project – one including data on risk modification of cardiovascular events and on risk modification of venous thromboembolism risk. The target audience would be primary care physicians, rheumatologists, gastroenterologists, cardiologists as well as physician-scientists with interest in atherosclerosis and autoimmune diseases.

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