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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.
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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
NCT00207675 - A Randomized, Multicenter, Open-label Study to Evaluate the Safety and Efficacy of Anti-TNF a Chimeric Monoclonal Antibody (Infliximab, REMICADE) in Pediatric Subjects With Moderate to Severe CROHN'S Disease
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
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

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 the dose of immunomodulators on pharmacokinetics of biologics: Patient level meta-analysis of randomized controlled trials

Narrative Summary:
Antibody-based therapies, termed biologics, are highly effective in treating immune disorders. Many patients, however, lose response to treatment due to the development of their own antibodies against the therapy. One method to prevent this problem is the co-administration of a second therapy to depress the immune system, an immunomodulator (IM). The optimal dose of IMs when used with biologics remains unknown. The proposed study

will look at the dose of IM and its impact on antibody formation against the biologic as well as the resultant efficacy of that therapy. The results of our study will allow us to better utilize biologic therapy to keep patients in durable, long-term remission.

Scientific Abstract:
Background; Biologics are efficacious in treating immune disorders. However, a proportion of patients have eventual loss of response due to immunogenicity against the biologic, which can be prevented by combination therapy with immunomodulators (IM). The optimal dose of IM when used in combination with biologics remains unknown.
Objective; To determine the optimal dose of IM when used in combination with biologics.
Study Design; Patient level data of clinical trials with infliximab (IFX) and golimumab (GO) will be analyzed. Patients will be categorized into those who received therapy as monotherapy or in combination with an IM (azathioprine (AZA)/methotrexate (MTX)). Those taking IM will be divided into high vs low AZA (? or <2.0 mg/kg) and high vs low MTX (? or <15 mg/week).
Participants; Patients with Crohn's disease, ulcerative colitis, rheumatoid arthritis and ankylosing spondylitis that participated in clinical trials of IFX and GO.
Main Outcome Measure(s); The primary outcome is trough level of IFX/GO measured at week 14. Secondary outcomes are trough level of IFX/GO measured at week 52, the incidence of anti-drug antibody, the rate of clinical remission, and the rate of adverse effects. These outcomes will be compared between patients on monotherapy and high or low AZA or MTX separately among each disease, and then will be summarized.
Statistical Analysis; Among each disease, the collected data will be summarized as a network meta-analysis, and rank of superiority will be analyzed between interventions.

Brief Project Background and Statement of Project Significance:
Biologic agents such as infliximab (IFX) have been shown to be highly efficacious in treating immune disorders such as inflammatory bowel disease and rheumatoid arthritis. A significant proportion of patients, however, have no initial response (primary non-response) or eventual loss of response (secondary loss of response) to therapy. It is thought that a majority of the cases of secondary loss of response are due to the formation of antibodies against the therapeutic agent, termed immunogenicity. One method to prevent immunogenicity is the concomitant treatment with an immunosuppressive drug such as azathioprine or methotrexate, referred to as combination therapy. Azathioprine or methotrexate are also used as the sole therapy to maintain remission in these diseases, and their dose is optimized based on the weight of the patient. The optimal dose of azathioprine or methotrexate when used in combination with a biologic therapy remains unknown. It is common for clinicians to administer relatively low doses of IMs in combination with biologic therapies in order to minimize side effects while decreasing the rate of immunogenicity, however no evidence exists to support this practice in inflammatory bowel disease. In a recently published retrospective study we showed that a higher dose of azathioprine was superior to a low dose in preventing immunogenicity against IFX in patients with ulcerative colitis. Patients receiving greater than 2.0 mg/kg of azathioprine had greater IFX levels than those receiving less than 2.0 mg/kg and those receiving IFX alone. Antibodies directed against IFX (ATI) were less common in patients receiving higher doses of IFX further supporting the hypothesis that higher levels of IFX were a result of decreased immunogenicity. The clinical outcome was superior in patients receiving high dose azathioprine while those taking low dose AZA had indistinguishable outcomes from those receiving IFX monotherapy.
It has been shown that combination therapy is superior to monotherapy with biologic agents in inflammatory bowel disease, but the optimal dose of IM in combination therapy has yet to be examined in a prospective study. We propose that this can be shown by looking at the data of previously published clinical trials with IFX and goliumumab. The proposed study will use individual patient level data from the clinical studies. Efficacy of interventions (monotherapy vs high or low AZA or MTX, respectively) will be assessed by network meta-analysis. The results of our study would have substantial impact as it will provide new insights for optimization of combination therapy that will allow patients to stay in durable long-term remission with biologics through effective prevention of immunogenicity.

Specific Aims of the Project:
Specific hypothesis:
We hypothesize that concomitant use of "high dose" immunomodulators (IM) with biologic therapy will be correlated with greater blood levels of the biologic than concomitant "low-dose" IM, or biologic monotherapy.

Primary aim:
AIM 1: To compare14-week biologic trough levels between patients receiving biologic therapy in one of five groups: monotherapy, with "low dose" azathioprine (< 2.0 mg/kg), or with "high dose" azathioprine (?2.0 mg/kg), with "low

dose" methotrexate (<15 mg/week), or with "high dose" methotrexate (?15 mg/week).

Secondary aim:
AIM 1: To compare 52-week biologic trough levels between patients in the five study groups.

AIM 2: To compare immunogenicity, as evidenced by the presence of antibodies against the biologic at 14 weeks after initiation of therapy, between patients in the five study groups.

AIM 3: To compare rates of clinical remission at week 14 and 52 between patients in the five study groups.

AIM 4: To identify a correlation between the weight based dose (mg/kg) of azathioprine/methotrexate and the biologic trough level by linear regression analysis.

AIM 5: Assess and compare the incidence of adverse reactions among the above five groups.

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
Participant-level data meta-analysis
Participant-level data meta-analysis uses only data from YODA Project

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:
Data Source: Patient level data from the clinical trials of infliximab and golimumab.
Inclusion Criteria: All patients who participated in the clinical trials of infliximab and golimumab.
Exclusion Criteria: Patients who did not complete the study or with insufficient data. Patients who changed the doses of immunomodulators during the study period.

Main Outcome Measure and how it will be categorized/defined for your study:
The main outcome is to compare week 14 biologic trough levels between patients receiving biologic therapy in one of five groups: monotherapy, with "low dose" azathioprine (< 2.0 mg/kg) or with "high dose" azathioprine (?2.0 mg/kg), with "low dose" methotrexate (<15 mg/week) or with "high dose" methotrexate (?15 mg/week). The trough biologic level of each patient will be collected. The mean level and its 95% CI will be calculated for each group.

Analysis will be done for each specific disease (Rheumatoid arthritis, Ankylosing spondyloarthrtis, Crohn's disease, Ulcerative colitis) and biologic (infliximab, golimumab).

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
The main independent variable is the level of concomitant immunosuppressant medication and will be divided into one of five groups: monotherapy, "low dose" azathioprine (< 2.0 mg/kg), "high dose" azathioprine (?2.0 mg/kg), "low dose" methotrexate (<15 mg/week), or "high dose" methotrexate (?15 mg/week).

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:
Secondary variables include the trough level of biologic therapy at 52 weeks, and will be collected as described above in the main outcome at the 52 week time point. Antibodies against infliximab or golimumab will be characterized as a binary variable of present or absent as demonstrated by specific laboratory evaluations for each of the five groups as described above. The clinical outcomes will be characterized as the number of patients in clinical remission at 14 and 52 weeks in each of the five study groups. Clinical remission is defined in rheumatoid arthritis as a sustained improvement of 50% from baseline using the American college of rheumatology (20) criteria. Remission in Crohn's disease is defined as a crohn's disease activity index <150. Remission in ulcerative colitis is defined as a sustained decrease in the Mayo ulcerative colitis score of at least 3 points and at least 30% from baseline. Our final secondary aim will use data collected above including weight based dosing of azathioprine in mg/kg, the dose of methotrexate per week, and the individual biologic therapy trough level at 14 and 52 weeks. The incidence of adverse reactions will be compared between groups.

Statistical Analysis Plan:

Analysis will be done separately for each disease and biologic. For example, Crohn's disease treated with infliximab, ulcerative colitis treated with golimumab, and so on. Patient level data of primary and secondary aims will be summarized for each treatment arm (monotherapy, high or low AZA or MTX), and will then be compared by network meta-analysis. This method will allow analyzing, simultaneously, three or more different interventions in one meta-analysis and to confirm the rank of superiority of treatment.

Project Timeline:
Estimated start date April 1, 2015 with analysis completion by October 1, 2015. Manuscript draft and submission by December 1, 2015. Results will be reported back to Yoda following manuscript revisions and acceptance, estimated April 1, 2016.

Dissemination Plan:
We expect the data analysis to result in preparation of a manuscript for publication in professional journals. Suitable journals include Gastroenterology, JAMA, or American journal of gastroenterology.

Bibliography:
1. Hayes, M. J., Stein, A. C. and Sakuraba, A. (2014), Comparison of efficacy, pharmacokinetics, and immunogenicity between infliximab mono- versus combination therapy in ulcerative colitis. Journal of Gastroenterology and Hepatology: 2014 Jun;29(6):1177-85.