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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

http://yoda.yale.edu/system/files/financial_disclosure_munizpedrogo.pdf
http://yoda.yale.edu/system/files/financial_disclosure_kashyap.pdf
http://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_murad.pdf
http://yoda.yale.edu/system/files/financial_disclosure_wang.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
Associated Trial(s):

1. NCT00036439 - A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients With Active Ulcerative Colitis
2. NCT00096655 - A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients With Active Ulcerative Colitis
3. 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
4. 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
5. 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
6. NCT00202865 - Evaluation of Low Dose Infliximab in Ankylosing Spondylitis (CANDLE)
7. 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)
8. NCT01551290 - A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Infliximab in Chinese Subjects With Active Ulcerative Colitis
9. NCT00771667 - A Phase 2b, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Ustekinumab Therapy in Subjects With Moderately to Severely Active Crohn's Disease Previously Treated With T
10. NCT01369329 - A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Subjects With Moderately to Severely Active Crohn's Disease Who Have Failed
11. NCT01369342 - A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Subjects With Moderately to Severely Active Crohn's Disease (UNITI-2)
12. NCT01369355 - A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Maintenance Therapy in Subjects With Moderately to Severely Active Crohn's Disease

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

Research Proposal

Project Title

Comparative efficacy of biologics in resolving extraintestinal manifestations of IBD: a systematic review and meta-analysis

Narrative Summary:

Extraintestinal manifestations (EIMs) are relatively common in patients suffering from inflammatory bowel disease (IBD). Several observational studies have reported the prevalence of at least one EIM to be around 6 – 47% among patients with IBD. More importantly, EIMs have been demonstrated to affect the quality of life of these patients and can even be associated with more comorbidity than the bowel disease itself. Numerous clinical trials have shown that biologics are effective in inducing and maintaining remission of bowel inflammation, but the comparative efficacy of currently available biologics in resolving EIMs remains unknown.

Scientific Abstract:

BACKGROUND: Extraintestinal manifestations (EIMs) can occur in up to 47% of patients that suffer from inflammatory bowel disease (IBD) and have been shown to negatively affect their quality of life. Our goal is to perform a systematic review and meta-analysis of the comparative efficacy of biologic therapy in resolving EIMs.
OBJECTIVE: To assess the comparative efficacy of biologic therapy in resolving EIMs of IBD by performing a systematic review and meta-analysis of randomized controlled trials (RCTs)
STUDY DESIGN: Systematic review and meta-analysis of RCTs
PARTICIPANTS: Adults over 18 years of age participating in any of the following RCTs: RCTs evaluating the efficacy of biologic therapy in inducing and/or maintaining remission of luminal inflammation in IBD; and RCTs evaluating the efficacy of biologic therapy in treating spondyloarthropathies in which patients with IBD were included.
MAIN OUTCOME MEASURES: For IBD trials, the main outcome measure is the proportion of patients that had resolved EIMs after treatment with a biologic compared to placebo. For spondyloarthropathy trials, the main outcome measure is the proportion of patients that achieved an ASDAS inactive disease score after treatment with a biologic compared to placebo.
STATISTICAL ANALYSIS: Data will be pooled in a random effects model and outcome measures will be expressed as relative risks (RR) with 95% confidence intervals. Risk of bias, subgroup, and sensitivity analyses will be performed as well as tests for heterogeneity to assess inconsistency between trials

Brief Project Background and Statement of Project Significance:

Extraintestinal manifestations (EIMs) are relatively common in patients suffering from inflammatory bowel disease (IBD), of which Crohn’s disease (CD) and ulcerative colitis (UC) are the main entities. Several observational studies have reported the prevalence of at least one EIM to be around 6 – 47% among patients with IBD, with higher susceptibility among those who smoke, have colonic involvement, and develop perianal CD. More importantly, some of the most common EIMs have been demonstrated to affect the quality of life in patients with IBD and can even be associated with more comorbidity than the bowel disease itself. Therefore, an early and proper management of EIMs is essential for improving the overall quality of life in patients with IBD.

The development of biologic therapy has markedly improved the quality of life of patients with IBD and biologics are now a mainstay in the management of moderate-to-severe IBD, particularly CD. TNF-? inhibitors, anti-?4-integrin antibodies, and one anti-interleukin-12/23 antibody have been shown to be effective in inducing and maintaining remission of luminal bowel inflammation in randomized controlled trials. However, most of the data regarding the efficacy of these biologics in treating EIMs has not been reported. Current recommendations for management of EIMs are based on the limited evidence available from case reports and open-label trials, and no specific guidelines have been developed for therapy. Although meta-analyses have been published for the efficacy of these drugs in treating luminal inflammation, no study assessing the comparative efficacy of currently available biologics for IBD in managing EIMs has been published.

The importance of developing more specific guidelines for the management of IBD with associated EIMs stems from the fact that some of these inflammatory manifestations can lead to irreversible deterioration and long-term disability if not treated early and effectively. Determining which of the currently available biologic therapies, if any, is the most effective option for managing patients with IBD complicated by EIMs will lead to long-term improvements in quality of life and significant reductions in long term morbidity. We therefore propose a systematic review of randomized controlled trials and meta-analysis to assess the comparative efficacy of biologic therapy in treating EIMs associated with IBD.

Specific Aims of the Project:

PRIMARY AIM: The primary aim of the study is to assess the comparative efficacy of currently available biologic therapies in resolving EIMs of IBD.

SECONDARY AIM: To compare the results on the efficacy of biologic therapy in resolving musculoskeletal manifestations from trials targeting spondyloarthropathies vs. the results from trials targeting IBD luminal inflammation as a way to evaluate the reliability of the assessments performed in IBD trials.

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 populationsParticipant-level data meta-analysisParticipant-level data meta-analysis will pool data from YODA

Project with other additional data sources

Research Methods

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

DATA SOURCE: We are requesting data regarding the presence of EIMs before and after therapy in each of the treatment arms of eligible RCTs. We are including two main groups of RCTs: RCTs evaluating the efficacy of biologic therapy in inducing and/or maintaining remission of bowel inflammation in patients with IBD (IBD trials); and RCTs evaluating the efficacy of biologic therapy in treating axial and/or peripheral spondyloarthropathies in which patients with concomitant IBD were included (spondyloarthropathy trials).

INCLUSION CRITERIA: 1) Adult IBD patients over 18 years of age with a diagnosis of CD or UC. 2) RCTs involving the following interventions: TNF-? inhibitors (infliximab, adalimumab, certolizumab pegol), anti-?4-integrin antibodies (natalizumab, vedolizumab), and anti-interleukin-12/23 antibodies (ustekinumab). 3) Subjects have to be randomized to treatment or placebo

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

For IBD trials, the main outcome measure is the proportion of patients that had resolved EIMs compared to baseline after treatment at specific time points. We are focusing on outcome measures obtained after 6 weeks of treatment in induction trials and after 52 weeks in maintenance trials. For spondyloarthropathy trials, the main outcome measure is the proportion of patients fulfilling ASDAS inactive disease criteria after treatment compared to baseline within the subgroup of IBD patients. For the latter, we are focusing on outcome measures obtained after 6 weeks of treatment.

We are requesting data on the following extraintestinal manifestations:
1) Musculoskeletal: peripheral arthropathy (type 1 and type 2), axial arthropathy (ankylosing spondylitis, sacroiliitis)
2) Ocular: uveitis, iritis, episcleritis
3) Dermatologic: erythema nodosum, pyoderma gangrenosum
4) Hepatobiliary: primary sclerosing cholangitis

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

The main independent variables are the biological therapies under study: infliximab, adalimumab, certolizumab pegol, natalizumab, vedolizumab, and ustekinumab. The dependent variables will be the proportion of patients that achieved resolution of EIMs after treatment with biologic therapy compared to placebo.

Statistical Analysis Plan:

SEARCH STRATEGY: We conducted a literature search using MEDLINE (1946 to February 2016), EMBASE (1988 to February 2016), and the Cochrane Central Register of Controlled Trials (Issue 2, February 2016).

CONTACT WITH STUDY SPONSORS: Studies fulfilling inclusion criteria will be added to the meta-analysis depending on the availability of unpublished data necessary to answer the research question. The respective study sponsors and data owners will be contacted in order to ensure that data on EIMs was collected before and after treatment.

DATA EXTRACTION: Data will be extracted as dichotomous outcomes and pooled into a software program designed for preparing and maintaining systematic reviews and meta-analyses (Review Manager 5.3; Nordic Cochrane Centre, Copenhagen, Denmark). Data will be extracted as intention-to-treat analyses, in which all dropouts are assumed to be treatment failures.

ASSESSMENT OF RISK OF BIAS: The assessment of risk of bias will be performed by two independent reviewers with any disagreements resolved by consensus with an expert investigator. Risk of bias will be assessed as described in the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0) by evaluating methods used for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, managing incomplete outcome data, selective reporting, and other biases.

DATA SYNTHESIS: Data will be pooled using a random effects model to give a more conservative estimate of the effect of individual therapies, allowing for heterogeneity between studies. The effects of different interventions will be expressed as a relative risk (RR) of achieving resolution in IBD trials or achieving ASDAS inactive disease criteria in spondyloarthropathy trials with 95% confidence intervals (CIs).

TESTS FOR HETEROGENEITY: To assess heterogeneity between individual therapies varying in dosing regimens and routes of administration, the I2 test statistic will be used. Values for I2 range from 0% to 100%, where 0% represents no observed heterogeneity and larger values represent increasing heterogeneity.

SUBGROUP ANALYSES
1. Drug vs. drug
2. TNF-? inhibitors vs. anti-?4-integrin antibodies vs. anti-interleukin-12/23 antibodies
3. Results from spondyloarthropathy trials vs. results from IBD trials
4. Subgroup analyses on response to therapy among individual categories of EIMs: musculoskeletal, skin, ocular, and hepatobiliary manifestations
5. Subgroup analyses for different dosages

SENSITIVITY ANALYSES: Sensitivity analyses will be performed for potential sources of heterogeneity between trials such as differences in the method of clinical evaluation of EIMs and differences in dosages.

Project Timeline:

The proposed project timeline began in 01/01/2016 with initial study design and ends in 12/31/2016 with final manuscript submission. In the first four months from 01/01/2016 to 04/30/2016 we have developed the study design, conducted the search strategy, performed the abstract screening, and finished the full-text review of eligible trials. We expect to have obtained all necessary unpublished data from eligible trials by 07/31/2016. Data analysis should be completed by 08/31/2016. Manuscript writing, review, and submission should be finished by 12/31/2016. Results will be reported back to the YODA Project by 12/31/2016.

Dissemination Plan:

Suitable journals for submission include Clinical Gastroenterology and Hepatology, Gut, and Inflammatory Bowel Diseases.

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