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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

http://yoda.yale.edu/system/files/colombel_yoda_project_coi_form_for_data_requestors_2016-signed.pdf
http://yoda.yale.edu/system/files/narula_yoda_project_coi_form_for_data_requestors_2016-signed.pdf
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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):

1. 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
2. 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
3. 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
4. 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

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

Research Proposal

Project Title

Use of TNF antagonist therapies with or without steroids for induction in Crohn's disease: A Meta-analysis

Narrative Summary:

Biologic agents, such as TNF antagonists, and corticosteroids are highly effective for induction of remission in Crohn's disease (CD) and ulcerative colitis (UC). Examination of data from a recent randomized controlled trial of combination therapy in patients with active CD (COMMIT) suggests that the addition of corticosteroids to infliximab may result in higher remission rates. However this possibility has not been evaluated by a dedicated RCT. Our objective is to perform a meta-analysis of existing induction trials of biologic therapies to assess whether adjunctive therapy with corticosteroids results in greater efficacy than biological monotherapy.

Scientific Abstract:

Background: Biologic agents, such as TNF antagonists, and corticosteroids are highly effective for induction of remission in Crohn's disease (CD) and ulcerative colitis (UC). Examination of data from a recent randomized controlled trial of combination therapy in patients with active CD (COMMIT) suggests that the addition of corticosteroids to infliximab may result in higher remission rates. However this possibility has not been evaluated by a dedicated RCT.
Objective: perform a meta-analysis of existing induction trials of biologic therapies to assess whether adjunctive therapy with corticosteroids results in greater efficacy than biological monotherapy. A secondary objective is to compare the safety of the two strategies.
Study Design: Meta-analysis of randomized control studies (RCTs) that fit search criteria
Participants: Study subjects in previously performed RCTs, age>18 years
Main Outcome Measure(s): The primary analysis will be a pooled summary estimate of clinical remission on anti-TNF therapy stratified by corticosteroid exposure at baseline. Secondary outcome to be measured are luminal response and safety of the two strategies.
Statistical Analysis: Standard meta-analysis methods will be used. The test of heterogeneity will be performed using the chi-squared test and the I2 test. Stratified analyses and meta-regression will be performed to explore factors that may explain heterogeneity between studies. This includes potential confounding factors such as disease severity (ex. Higher CDAI, CRP levels) or concurrent immunomodulator use.

Brief Project Background and Statement of Project Significance:

Biologic agents, such as TNF antagonists, and corticosteroids are highly effective for induction of remission in Crohn's disease (CD) and ulcerative colitis (UC). Examination of data from a recent randomized controlled trial of combination therapy in patients with active CD (COMMIT) suggests that the addition of corticosteroids to infliximab may result in higher remission rates. However this possibility has not been evaluated by a dedicated RCT. Our objective is to perform a meta-analysis of existing induction trials of biologic therapies to assess whether adjunctive therapy with corticosteroids results in greater efficacy than biological monotherapy. A secondary objective is to compare the safety of the two strategies.

Specific Aims of the Project:

The primary aim of the project is to assess whether adjunctive therapy with corticosteroids results in greater efficacy than biological monotherapy. We have performed a systematic literature review and will now perform a meta-analysis of relevant data.

We hypothesize that patients with CD treated with anti-TNF agents will have a higher response rate if treated concomitantly with corticosteroids for induction of remission, without significant differences in the risk of adverse events.

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 populationsNew research question to examine treatment safetySummary-level data meta-analysis will pool data from YODA Project with other additional data sourcesParticipant-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:

A systemic review was performed of Medline, Central and Embase for all English language studies in adult patients with Crohn's disease studying the efficacy of either adalimumab, certolizumab pegol, golimumab, and infliximab. Abstracts were included in the search in addition to a hand search to identify randomized controlled trials (manuscripts and abstracts).

Inclusion criteria:
• Randomized, placebo-controlled trials in which patient level data (case report forms) is obtainable and information regarding length and dosing of concurrent steroids
• Adult patients with Crohn's disease
• Anti-TNF agent used includes any of Infliximab, adalimumab, certolizumab pegol, and golimumab
• Duration of 4-12 weeks for induction
• Data available for remission rates at a short time interval (i.e. between 4-12 weeks)

We have identified 16 full text articles that are eligible for our study. In order to meet the aim of our study, non-published patient level data must be obtained.

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

The primary analysis will be a pooled summary estimate of clinical remission on anti-TNF therapy stratified by corticosteroid exposure at baseline. Patients with high dose concurrent steroid use (as defined in the inclusion criteria) will be analyzed separately from those with low concurrent steroid use. In this main analysis, all anti-TNF agents will be combined and will be evaluated based on remission at induction (between 4-12 weeks).

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

Many patients are treated with a weaning course of corticosteroids at the time of induction, so those patients who received the equivalent of >20mg daily of prednisone or equivalent during the first four weeks of induction treatment will be analyzed in the concomitant high-dose steroid therapy group. Those treated with <20mg daily of prednisone or equivalent during the first four weeks of induction will be analyzed in the concomitant low-dose steroid therapy group. Those who received no concurrent steroids will be analyzed in the no steroid group. Data will

also be collected on patients in the placebo arms who received concomitant high dose steroids, low dose steroids, or no steroids, as per the definitions above.

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

A secondary outcome that will be evaluated is luminal response. Response is measured differently between studies, but most commonly for CD will be based on a decrease in the Crohn's disease activity index (CDAI). Studies that report outcomes at weeks 4-12 will be combined irrespective of the duration of the induction period. To account for differences in steroid use between studies (i.e forced tapering, fixed dose, etc), the average daily dose of steroids used during the first four weeks of induction will be used to classify patients. An average daily dose of 20mg or more of prednisone will be considered high concurrent corticosteroid use. An average dose of less than 20mg of prednisone per day will be considered low dose. Safety will also be evaluated based on the same stratification and will include infusion/injection site reactions, malignancy, infections, and death.

Statistical Analysis Plan:

Statistical analyses will be performed by a PhD biostatistician, Dr. Emilia Bagiella (Mount Sinai, NY). The main analysis will be based on the intention-to-treat population from each study. The test of heterogeneity will be performed using the chi-squared test and the I2 test. The I2 test describes the percentage of variability in effect estimates that is due to heterogeneity rather than chance, wherein an I2 test greater than 50% suggests significant heterogeneity. A random effects model will be used assuming that heterogeneity will exist between studies; if the study data meet the criteria for homogeneity then a fixed effects model will be used. Stratified analyses and meta-regression will be performed to explore factors that may explain heterogeneity between studies. This includes potential confounding factors such as disease severity (ex. Higher CDAI, CRP levels) or concurrent immunomodulator use. Publication bias will be assessed using a funnel plot.

Sensitivity analyses (analyses to be run removing certain studies to see how it affects the results)
• Other sensitivity analyses may be run if there are outlier studies with unique design characteristics that appear to have a strong influence on the results (standard according to the Cochrane Handbook, section 9.7)

Subgroup analyses
• No concurrent immunomodulator versus immunomodulator-treated patients
• Individual anti-TNF agents will be compared with or without steroids, but not against each other

In addition to the 4 studies requested from YODA, data from for the following 12 studies have been requested from AbbVie, UCB, and Dr. Farrell. Of note, IPD will not be pooled within the data sharing platform.

1. Farrell, R. J., et al. (2003). "Intravenous hydrocortisone premedication reduces antibodies to infliximab in Crohn's disease: A randomized controlled trial." Gastroenterology 124(4): 917-924.
2. Colombel, J., et al. (2007). "Adalimumab for Maintenance of Clinical Response and Remission in Patients With Crohn's Disease: The CHARM Trial." Gastroenterology 132(1): 52-65.
3. Dewint, P., et al. (2014). "Adalimumab combined with ciprofloxacin is superior to adalimumab monotherapy in perianal fistula closure in Crohn's disease: A randomised, double-blind, placebo controlled trial (ADAFI)." Gut 63(2): 292-299.
4. Hanauer, S. B., et al. (2006). "Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: The CLASSIC-I trial." Gastroenterology 130(2): 323-332.
5. Rutgeerts, P., et al. (2012). "Adalimumab induces and maintains mucosal healing in patients with Crohn's Disease: Data from the EXTEND trial." Gastroenterology 142(5): 1102-1111.
6. Sandborn, W. J., et al. (2007). "Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial." Annals of internal medicine 146(12): 829-838.
7. Watanabe, M., et al. (2012). "Adalimumab for the induction and maintenance of clinical remission in Japanese patients with Crohn's disease." Journal of Crohn's & colitis 6(2): 160-173.
8. Sandborn, W. J., et al. (2007). "Certolizumab pegol for the treatment of Crohn's disease." New England journal of medicine 357(3): 228-238.
9. Sandborn, W. J., et al. (2010). "Certolizumab pegol in patients with moderate to severe Crohn's disease and secondary failure to infliximab." Clinical Gastroenterology & Hepatology 8(8): 688-695.
10. Sandborn, W. J., et al. (2011). "Certolizumab Pegol for Active Crohn's Disease: A Placebo-Controlled, Randomized Trial." Clinical gastroenterology and hepatology 9(8): 670-678.

11. Schreiber, S., et al. (2005). “A randomized, placebo-controlled trial of certolizumab pegol (CDP870) for treatment of Crohn's disease.” Gastroenterology 129, 807-818.
12. Schreiber, S., et al. (2007). “Maintenance therapy with certolizumab pegol for Crohn's disease.” New England journal of medicine 357, 239-250.

Project Timeline:

We have already performed a systematic literature review and have identified randomized control trials that fill our inclusion criteria. We have extracted all relevant published data but much data is still missing. Once access to study data is granted, we anticipate data extraction and analysis to take no longer than 2 months. Manuscript drafting will take another 1 month. Manuscript submission is aimed to take place no later than September 2016.

Dissemination Plan:

The results of this meta-analysis is anticipated to be of great interest to all IBD clinicians. A manuscript will be submitted about 3 months after data acquisition. As such, we plan to submit our manuscript to Gastroenterology, American Journal of Gastroenterology or Clinical Gastroenterology and Hepatology.

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