General Information

Key Personnel (in addition to PI):
  First Name: Kelly
Last name: Cushing
Degree: MD
Primary Affiliation: Massachusetts General Hospital
SCOPUS ID: 57188558444

  First Name: Tomer
Last name: Adar
Degree: MD
Primary Affiliation: Massachusetts General Hospital
SCOPUS ID:

  First Name: David
Last name: Cheng
Degree: AM
Primary Affiliation: Harvard University
SCOPUS ID:

  First Name: Tianxi
Last name: Cai
Degree: ScD
Primary Affiliation: Harvard University
SCOPUS ID:

  First Name: Siddharth
Last name: Singh
Degree: MD, MS
Primary Affiliation: University of California San Diego
SCOPUS ID:

  First Name: James
Last name: Proudfoot
Degree: MS
Primary Affiliation: University of California San Diego
SCOPUS ID:

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/conflictofinterest_aa_1.pdf
http://yoda.yale.edu/system/files/conflictofinterest_kc.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. 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. 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
5. 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
6. 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
7. 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
8. 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)
9. 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
10. NCT01190839 - Prospective, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial Comparing REMICADE (Infliximab) and Placebo in the Prevention of Recurrence in Crohn's Disease Patients Undergoing Surgical Resection Who Are at Increased Risk of
11. NCT00269854 - A Placebo-Controlled, Dose-Ranging Study Followed by a Placebo-Controlled, Repeated-Dose Extension of Anti-TNF Chimeric Monoclonal Antibody (cA2) in the Treatment of Patients With Active Crohn's Disease
12. Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease.
13. 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
14. 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
15. 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)
16. NCT00488631 - 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
17. 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

Impact of Age on Safety and Efficacy of Biologic Therapy for Inflammatory Bowel Disease

Narrative Summary:

Inflammatory Bowel Disease (IBD) encompasses two immune-mediated gastrointestinal tract diseases, Crohns Disease (CD) and Ulcerative Colitis (UC). Untreated disease can lead to chronic sequela of inflammation such as strictures, fistulas, dysplasia, and/or need for bowel resection. The incorporation of biologic therapy into practice has improved medical management of IBD. However, there is limited data on the efficacy and safety of these medications in high risk groups. This study proposes utilizing the repository of biologic trial data to evaluate the efficacy and safety of these medications in the elderly.

Scientific Abstract:

Background: The elderly represent a high risk group of patients with IBD. As such, efficacy and safety data of biologic therapy is needed. Objective: Define efficacy and safety of biologics in adults > 60 years. Study Design: Participants will be grouped by cases (adults > 60 years) and controls (adults < 60 years). The primary outcome evaluated will be absolute and relative clinical efficacy. Secondary endpoints will include absolute and relative clinical response, endoscopic healing, adverse events, antibody formation, and health-related quality of life. Clinical response will be defined as a decrease in CDAI by ? 100 in CD and Mayo score >2 with all sub-scores ? 1 in UC. Endoscopic healing will be assessed by the Mayo endoscopic sub-score for UC and gross endoscopic findings for CD. Health-related quality of life will be measured by the short form of the IBD Questionnaire (SIBD-Q) score. Participants: Adults > 60 years will be included as cases. All other participants (<60 years) will be included as controls. Main Outcome Measures: The main outcome measures include clinical efficacy, clinical response, and rates of adverse events. Additional outcomes of interest include endoscopic healing, antibody formation, and health-related quality of life. Statistical Analysis: Comparison of variables will be performed by t, Mann Whitney, Chi Square or Fisher Exact Test, as appropriate. Random effects model with meta regression, adjusting for potential confounders, will be used to examine the effect of age on efficacy and safety of biologic therapies in IBD.

Brief Project Background and Statement of Project Significance:

It is estimated that 10 to 30% of patients with IBD are over the age of 60.(1) These patients represent an important group for further study in IBD because their management requires additional considerations. First, the disease presentation and course may be different across age groups. A population based cohort study of IBD in France, EPIMAD, investigated differences in the natural history of IBD by age.(2) Results of this study demonstrated that older patients with CD tended to present more often with rectal bleeding and anal fistulas whereas younger patients tended to present more often with diarrhea and abdominal pain. In addition, the disease distribution in CD was more often colonic and the behavior more often inflammatory in older adults. Finally, the rate of disease behavior progression over 15 years was relatively low (9%), which may suggest a more indolent course. Alternatively, older patients with UC tended to present less often with rectal bleeding and abdominal pain and their disease distribution was more commonly left sided with 16% having some level of disease progression. Next, with increasing age comes the potential for additional complications both independently and related to increasing co-morbidities and polypharmacy.(1) Older patients with IBD-related hospitalization had an independently higher mortality when compared to younger patients, regardless of concurrent co-morbidity (OR 3.91).(3) These results highlight the independently deleterious effect age can have in IBD. In addition, older patients may have increasing cardiovascular, pulmonary, or metabolic disease, which can add complexity to decision making. Finally, the existing literature on biologic use in the elderly is limited. A retrospective review of anti-TNF efficacy demonstrated similar rates of clinical remission among those older and those younger than 65.(4) Lobaton, et al also demonstrated equivalent anti-TNF efficacy over the long term but showed lower efficacy in the short term.(5) Alternatively, Ananthakrishnan et al found lower efficacy in older patients when compared to younger patients.(6) Interpretation of retrospective studies is difficult and maintenance anti-TNF therapy is still reported to be low in the elderly; 9% in CD and 1% in UC.(1) Furthermore, older patients have been demonstrated to be three times more likely to stop therapy, with 70% discontinuing therapy after just over two years.(6) Low rates of use may be related to hesitancy by prescribers to use immune suppressive drugs in this higher risk population. Such concerns are supported by a reported rate of infectious adverse events of 11% in the elderly on anti-TNF therapy.(4) Interpretation of primary clinical trial data may offer additional insight into clinical efficacy and safety. Unfortunately, published clinical trial

data in the elderly is limited by the small absolute number of participants as well as the lower average age of participants.(7) In summary, there is a need for more data evaluating the efficacy and safety of biologic treatment in the elderly and composite clinical trial data may allow for more accurate reflections of efficacy and safety.

Specific Aims of the Project:

1) The primary aim of this study will be to compare absolute and relative clinical efficacy rates of biologic therapy across the strata of age (>60 yrs versus < 60 yrs). Absolute clinical efficacy will be assessed by the absolute difference in rates of clinical remission between older patients with any biologic therapy and placebo compared to younger patients with any biologic therapy and placebo. Relative efficacy will be assessed as the crude difference between older and younger patients on biologic therapy.
2) The secondary aim of this study will be to compare absolute and relative safety rates of biologic therapy across the strata of age (>60 yrs versus <60 yrs). Safety outcomes of interest will include serious adverse events, infection related adverse events and malignancy. Absolute safety rates will be assessed by the absolute difference in rates of events between older patients on any biologic therapy and placebo compared to younger patients on any biologic therapy and placebo. Relative safety rates will be assessed as the crude difference between older and younger patients on biologic therapy.
3) Additional endpoints of interest will include absolute and relative clinical response, endoscopic healing, adverse events, rates of antibody formation, and quality of life

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 safety

Research Methods

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

The database will be queried for all clinical trial data evaluating efficacy and safety of biologic therapy in CD or UC. Based on a preliminary evaluation of the data available on the website, we expect to procure data related to infliximab, golimumab, and ustekinumab use. Additional drugs of interest, should they become available in the interim, would include adalimumab, certolizumab, vedolizumab, mercaptopurine, azathioprine, and/or methotrexate. All patients included in the original clinical trial data will be included in this sub-analysis. No patients will be excluded.

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

The main outcome measure evaluated will be clinical remission. Clinical remission will be defined as a CDAI score less than 150 for CD and a Mayo Score less than 2 for UC. Clinical remission will be measured as an absolute difference (older patients with any biologic therapy versus placebo compared to younger patients with any biologic therapy versus placebo) and relative difference (older patient on any biologic therapy versus younger patient on any biologic therapy). The secondary outcome measure will be safety. Safety outcomes of interest will include serious adverse events, infection related adverse events, and malignancy. Absolute safety rates will be assessed by the absolute difference in rates of events between older patients on any biologic therapy and placebo compared to younger patients on any biologic therapy and placebo. Relative safety rates will be assessed as the crude difference between older and younger patients on biologic therapy.

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

The main predictor variable will be age.

• Cases will be defined as adults greater than or equal to 60 years of age.
• Controls will be defined as adults less than 60 years of age.

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

Additional variables of interest will include absolute and relative differences in clinical response, endoscopic healing, antibody formation, and health-related quality of life. Clinical response will be defined as a decrease in

CDAI by greater than or equal to 100 in CD and a decrease in the Mayo score by 2 (with all subscores less than or equal to 1) in UC. Endoscopic activity will be defined as mucosal healing: a Mayo endoscopic subscore of 0 or 1 for UC and absence of ulcers in CD. Antibody formation will be assessed by trough drug level and detectable antibodies. Finally, health-related quality of life will be assessed with the SIBD-Q score.

Statistical Analysis Plan:

Comparison of continuous variables will be performed by t tests or Mann-Whitney test, as appropriate. Comparison of categorical variables will be performed by Chi square tests or Fisher Exact tests, as appropriate. Random effects model with meta regression of potential confounders (type of biologic [anti-TNF versus IL-23], type of disease [CD versus UC], and presence or absence of concomitant immunosuppression) will be used to examine the effect of age on clinical efficacy and safety of biologic therapies in the management of IBD.

Project Timeline:

Anticipated Project Start Date: August 1, 2017
Analysis Completion Date: March 31, 2018
Report of Results to YODA: May 31, 2018
Date of First Manuscript Draft: June 1, 2018
Date of Manuscript Submission: August 1, 2018

Dissemination Plan:

The expected audience for this work includes practicing general gastroenterologists and IBD sub-specialists. Potential journals for submission include Inflammatory Bowel Disease and the Journal of Crohn's and Colitis.

Bibliography:

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Supplementary Material:

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