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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?: Data Holder (Company)

Conflict of Interest

https://yoda.yale.edu/system/files/laurent_coi_0.pdf
https://yoda.yale.edu/system/files/chen_minhu-coi_0.pdf
https://yoda.yale.edu/system/files/coi-jing_guo_0.pdf
https://yoda.yale.edu/system/files/hibi_coi.pdf
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https://yoda.yale.edu/system/files/coi_form_ruslan_sergienko.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

1. NCT00036439 - C0168T37 - A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients With Active Ulcerative Colitis
2. NCT00096655 - C0168T46 - A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients With Active Ulcerative Colitis
3. NCT00094458 - C0168T67 - 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 Therapy (Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease)
4. NCT00487539 - C0524T17 - 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 - C0168T21 - 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. NCT00537316 - P04807 - 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)
7. NCT01551290 - CR018769 - A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Infliximab in Chinese Subjects With Active Ulcerative Colitis
8. NCT00488631 - C0524T18 - 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

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

Research Proposal

Project Title

Meta-analysis: Duration of inflammatory bowel disease and its impact on efficacy of biologic drugs

Narrative Summary:

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory diseases of the gut, that can culminate in complications requiring abdominal surgery. Novel effective biologic therapies may change this natural history and there is some evidence that earlier use of biologic drugs is more beneficial than their introduction later after convnetional drugs have failed. We aim to perform metanalysis of all trials of biologic drugs for CD and UC, to examine if response and remission rates achieved in patients with short-term disease is better than in long disease duration. If indeed so, it may provide important support for earlier use of biologic drug as a preferred therapeutic strategy.

Scientific Abstract:

Background: Post-hoc sub-group anlayses suggested a better response to anti-TNF treatment in patients with shorter Crohn's disease duration as compared with patients with longer disease duration. However, no systematic evaluation of this correlation has been performed, and data for ulcerative colitis (UC) is lacking.
Aim: The aim of the present study is to analyze if there is a correlation between the rate of response to biologic treatment and the duration of disease at treatment initiation.
Study design: A meta-analysis of all published randomized placebo-controlled clinical trials of FDA-approved

biologics in IBD will be performed.
Participants: Patients included in RCTs of approved anti-TNFs or anti-integrin drugs for IBD
Main outcomes measures: The primary outcome will be the rate of induction of remission in patients with disease duration<18 months (short disease) compared to those with >18 months duration (late disease). Secondary analyses will be response to induction, response and remission at end of maintenance phase and colectomy rate (in UC only) for short versus long-term disease, as well as the rate of primary outcome in anti-TNF and in anti-integirn trials. All analyses will be performed separately for UC and CD. Additional exploratory analyses will compare outcomes for disease duration cut-offs of 3 and 5 years.
Statistical analysis: This will be a meta-analysis. Protocolized data extraction will be done and data will be pooled using a random effects model. We will perform risk of bias assessment, and express outcomes by odds ratios

Brief Project Background and Statement of Project Significance:

Background : The chronic relapsing-remitting course of Crohn’s disease (CD), with ensuing bowel damage, is believed to be responsible for a possible reduced rate of response to anti-TNF in patients with long disease duration, as reported in some studies. However, no systematic analysis of all available clinical trials was hitherto performed to examine the correlation of CD duration with response to anti-TNF, or with the response to any biologic drug in general. Moreover, only scant data is available pertaining to such possible correlation in ulcerative colitis (UC). This comprises a knowledge gap in our understanding of optimal therapeutic strategies, and in particular, the role of institution of biologic drugs at an early phase of disease as a window of opportuinty whereby response to therapy will be optimal and will facilitate arresting disease progression and altering its natural history. Thus, the hereby proposed meta-analysis will provide important and novel systematic insight about the correlation between IBD disease duration and response to biologic therapy. Such information may prove to have important and wide impact on the choice of therapeutic strategies for IBD patients and their timing, and in particular for decisions regarding top-down versus step-up approaches.
1.Schreiber S, et al. Increased response and remission rates in short-duration Crohn’s disease with subcutaneous certolizumab pegol: an analysis of PRECiSE 2 randomized maintenance trial data. Am J Gastroenterol 2010; 105:1574–1582
2.Schreiber S , et al. Maintenance therapy with certolizumab pegol for Crohn?s disease . N Engl J Med 2007 ; 357 : 239 – 50.
3. Ananthakrishnan AN, Binion DG: Editorial: improved efficacy of biological maintenance therapy in "early" compared with "late" Crohn's disease: strike while the iron is hot with anti-TNF agents? Am J Gastroenterol 2010, 105:1583-1585.
4. Colombel JF et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med 2010, 362:1383-1395.
5. Schreiber S et al. Subgroup analysis of the placebo-controlled CHARM trial: increased remission rates through 3 years for adalimumab-treated patients with early Crohn's disease. J Crohns Colitis 2013, 7:213-221.

Specific Aims of the Project:

The aim of the present study is to perform a meta-analysis of the impact of disease duration on the efficacy of FDA approved biologics for CD and UC (infliximab, adalimumab, golimumab, certolizumab, vedolizumab and natalizumab), using randomized placebo controlled trials or immuno-modulator/biologic combination randomized controlled trials. The primary outcome will be the rate of remission at the end of induction (week 4-14) in patients with short disease duration <18months, as defined by the IOIBD (Peyrin-Biroulet, AJG 2012), compared to patients with longer duration of disease. The definition of the primary outcome will be a CDAI<150 or Mayo?2 with no individual subscore>1 for CD and UC, respectively. Additional outcomes will be the rate of response to induction and rate of response and remission at the end of the maintenance phase (when applicable). All outcomes will be analyzed separately for CD and UC. An additional outcome for UC patients will be the rate of colectomy for patients with short and long-durion. Because of the arbitrary nature of short disease defintion, additional analyses will prgmatically define short disease duration as <3 years or as <5 years. We hypothesize a better response to biologics in patients with early short-term disease.

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
Confirm or validate previously conducted research on treatment effectiveness
Summary-level data meta-analysis pooling data from YODA Project with other additional data sources
Participant-level data meta-analysis

Participant-level data meta-analysis pooling 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:

Eligible studies will be randomized placebo controlled IBD trials of biologics which are approved by the FDA for IBD treatment (anti-TNFs and/or anti-integrins), or RCTs comparing biologic-immunomodulator combination treatment versus immunomodulator alone (with placebo biologic). To be included, trials outcomes should include clinical efficacy measures as one of the end-points assessed and reported (i.e. purely pharmacokinetic or safety trials not assessing clinical efficacy will be excluded). CD trials for indications other than active luminal CD will be excluded. Discontinuation and post-surgical prophylaxis trials will be excluded. Duration of biologics therapy will have to be at least two doses of induction spanning = 2 weeks. Therefore, trials using a single infusion or injection of a biologic will be ineligible. A trial employing a single infusion/injection for induction, whether randomized or not, followed by randomization for maintenance phase will be eligible for analysis restricted to efficacy outcomes of the maintenance treatment phase. Studies investigating dosing which are not approved for clinical practice or exploring non-approved indications will be also excluded.

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

The primary outcome will be the rate of remission of the active arm over the placebo arm at the end of the trial induction (week 4-14) for patients with short disease duration compared to patients with long duration of disease. This choice of primary outcome stems from the hypothesis that primary response more closely reflects the biology of underlying IBD and its modulation by duration of disease, compared to response during maintenance (which is confounded by factors unrelated to disease biology per se, such as immunogenicity). The definition of the primary outcome will be a CDAI<150 or Mayo?2 with no individual subscore>1 for CD and UC, respectively, in patients with short versus long duration of disease. In trials employing other clinical scores, the preimary outcome will be evaluated as per the score used in the specific trial, but a senstivity analyses will eb perfomrd excluding all trials which did not employ the pre-specified measures for remission.

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

The main predictor variable will be disease duration.The definition of short-disease duration (‘early disease’) is somewhat arbitrary given the absence of evidence or biologic markers that are able to delineate the underlying biology of early disease and distinguish it from late disease.Published trials and expert opinion definitions of ‘early disease’ range between 1-5 yrs since onset [Schreiber S, AJG 2010, Schreiber S, N Engl J Med 2007, Ananthakrishnan AN, AJG 2010, Colombel NEJM 2010].A recent IOIBD working group pragmatically defined early CD as one that is ?18 mos in duration (Peyrin-Biroulet L, AJG 2012).Thus, the present meta-analysis will employ the IOIBD disease duration time-point of 18 mos to define early disease.However, bearing in mind the chronic life-long course of IBD, the diverse definitions existing, the possibility that patients enrolled into clinical trials at such early stage of their disease are a unique patient group, and the paucity of pts with<18 months of disease in trials, we will perform two additional analyses pragmatically defining disease duration cut-offs at 3 and at 5 yrs to delineate short vs long-term disease.

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

Other variables explored will be the class of the biologic used (assessing the disease-duration correaltion with indeuction of remission in anti-TNF trials analyzed jointly, and in anti-integrins trials jointly), and the prior TNF exposure status (Sensitivity analysis will be performed including only trials which exclusively enrolled biologic-naive patients). Additional co-variate will be the impact of concomitant immunomodulator, assessed by sub-analysis excluding trials with >40% of the population being terated with immunomodulators. The type of IBD will also be a co-varaite, but as noted, we will a-priori address this important variable by performing all analyses separately for UC and CD.

Statistical Analysis Plan:

Two investigators will independently assess the risk of bias as described in the Cochrane Handbook for Systematic

Reviews of Interventions (Higgins JPT et al, Cochrane handbook for systematic reviews of interventions: version 5.0.0, 2008). We will use the GRADE criteria to assess the overall quality of evidence used for specific outcomes. As we will include Evidence from randomized controlled trials all data will begin as high quality evidence. However, they can then be downgraded due to: (1) risk of bias from the studies, (2) indirect evidence, (3) inconsistency (unexplained heterogeneity), (4) imprecision in data, and (5) publication bias. Data will be pooled using a random effects model, to give a more conservative estimate of the likelihood of benefit of biologics in short-term disease, allowing for any heterogeneity between studies [DerSimonian R, et al, Control Clin Trials 1986]. As the outcomes are dichotomous data, we will use the Odds Ratio (OR) and extract a single data set from each study for further analysis. Pooled results will be expressed as odds ratio for the respective outcome for biologics versus placebo arm, for patients with short disease duration compared to those long duration of disease, with 95% confidence intervals (CI). Inconsistency will be quantified with a statistical test of heterogeneity. A two-sided p value less than 0.05 will be considered statistically significant. Stata version 14.0 will be used for all statistical analyses and to generate Forest plots of pooled RRs with 95% CIs, as well as funnel plots. The latter will be assessed for evidence of asymmetry using the using the Egger test, if sufficient (?10) eligible studies. A full SAP can be found in Supplementary Material.
Software Used:
R

Project Timeline:

1st March – Complete submission of revised data requests to data-sharing websites
31st June – Retrieval of all data. Data set locking
31st September – completion of analysis
31st November - Manuscript drafting and submission

Dissemination Plan:

If this systematic analysis indeed shows there is a tangible benefit for use of biologics early after disease onset rather than at later disease stages, this may comprise an important step forward in our therapeutic strategies aiming to optimize the therapy of IBD and to improve the care of patients with these chronic inflammatory conditions. The results of this study will be disseminated to patients and care-givers by variety of routes including disease-specific educational websites, publication in medical journals as well as in general press, and distribution to patients' societies.

Bibliography:

1.Schreiber S, et al. Increased response and remission rates in short-duration Crohn's disease with subcutaneous certolizumab pegol: an analysis of PRECiSE 2 randomized maintenance trial data. Am J Gastroenterol 2010;105:1574–1582
2.Schreiber S , et al. Maintenance therapy with certolizumab pegol for Crohn?s disease . N Engl J Med 2007 ; 357:239 – 50.
3. Ananthakrishnan AN, Binion DG: Editorial: improved efficacy of biological maintenance therapy in "early" compared with "late" Crohn's disease: strike while the iron is hot with anti-TNF agents? Am J Gastroenterol 2010,105:1583-1585.
4. Colombel JF et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med 2010, 362:1383-1395.
5. Schreiber S et al. Subgroup analysis of the placebo-controlled CHARM trial: increased remission rates through 3 years for adalimumab-treated patients with early Crohn's disease. J Crohns Colitis 2013, 7:213-221.
6. Peyrin-Biroulet L, et al. Development of the Paris definition of early Crohn's disease for disease-modification trials: results of an international expert opinion process. Am J Gastroenterol. 2012 Dec;107(12):1770-6

Supplementary Material:

https://yoda.yale.edu/sites/default/files/sap-yoda_feb_2016.docx
https://yoda.yale.edu/sites/default/files/data_tables_0.docx
https://yoda.yale.edu/sites/default/files/manuscript.pdf