Principal Investigator

First Name: Shomron
Last Name: Ben-Horin
Degree: MD
Primary Affiliation: First Affiliated Hospital of Sun Yat-Sen University
E-mail: novack@bgu.ac.il
Phone number: (972)507113599
Address:
Zhongsahn 2 Ave
City: Guangzhou
State or Province: Guangdong Province
Zip or Postal Code: 510080
Country: China

General Information

Key Personnel (in addition to PI):

First Name: Shomron
Last name: Ben-Horin
Degree: MD
Primary Affiliation: Sun Yatsen 1st affiliated Hospital, Guangzhou China

First Name: Yue
Last name: Zhao
Degree: MD
Primary Affiliation: Department of Gastroenterology, First affiliated Hospital of the Sun Yatsen University, Guangzhou, China

First Name: Jing
Last name: Guo
Degree: MD
Primary Affiliation: Department of Gastroenterology, First affiliated Hospital of the Sun Yatsen University, Guangzhou, China

First Name: Ren
Last name: Mao
Degree: MD
Primary Affiliation: Department of Gastroenterology, First affiliated Hospital of the Sun Yatsen University, Guangzhou, China

First Name: Ruslan
Last name: Sergienko
Degree: MA
Primary Affiliation: Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

First Name: Jian
Last name: Zhang
Degree: MD
Primary Affiliation: Department of Gastroenterology, Sheba Medical Center, Sackler School of Medicine, Tel-Aviv University, Tel Aviv, Israel

First Name: Taku
Last name: Kobayashi

Degree: MD
Primary Affiliation: Department of Gastroenterology, Kitasato Institute Hospital, Tokyo, Japan

First Name: Toshifumi
Last name: Hibi
Degree: MD
Primary Affiliation: Department of Gastroenterology, Kitasato Institute Hospital, Tokyo, Japan

First Name: Yehuda
Last name: Chowers
Degree: MD
Primary Affiliation: Department of Gastroenterology, Rambam Health Care Campus, Haifa

First Name: Jean Frederic
Last name: Colombel
Degree: MD
Primary Affiliation: Helmsley Inflammatory Bowel Disease Center, Icahn School of Medicine, Mount Sinai Hospital, New York, New-York, U.S.A

First Name: Laurent
Last name: Peyrin-Biroulet
Degree: MD
Primary Affiliation: Department of Gastroenterology, Inserm U594, Nancy University Hospital, France

First Name: Gilaad
Last name: Kaplan
Degree: MD
Primary Affiliation: Department of Gastroenterology, University of Calgary, Calgary, Canada

First Name: Min-hu
Last name: Chen
Degree: MD
Primary Affiliation: Department of Gastroenterology, First affiliated Hospital of the Sun Yatsen University, Guangzhou, China

First Name: Lena
Last name: Novack
Degree: PhD
Primary Affiliation: Ben-Gurion University

Are external grants or funds being used to support this research?: External grants or funds are being used to support this research.
Project Funding Source: This work was supported in part by the 'Talpiot' medical leadership grant from the Sheba Medical Center (to SBH)
How did you learn about the YODA Project?: Other

Conflict of Interest

https://yoda.yale.edu/system/files/coi_by_sbh.pdf
https://yoda.yale.edu/system/files/chen_minhu-coi_1.pdf
https://yoda.yale.edu/system/files/coi_kaplan_yoda_project_jan_2016_0.pdf
https://yoda.yale.edu/system/files/coi_form_ln_0.pdf
https://yoda.yale.edu/system/files/guo-coi_0.pdf
https://yoda.yale.edu/system/files/jf_colombel_coi_form_for_data_requestors_2016-signed.pdf
https://yoda.yale.edu/system/files/jian_zhang-coi_1.pdf
https://yoda.yale.edu/system/files/kobyashi_and_hibi_coi_0.pdf
https://yoda.yale.edu/system/files/laurent_coi_2.pdf

https://yoda.yale.edu/system/files/mao_ren_coi_1.pdf
https://yoda.yale.edu/system/files/ruslan_coi_form_rs.pdf
https://yoda.yale.edu/system/files/yc-coi_1.pdf
https://yoda.yale.edu/system/files/zhao-coi_1.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; REMICADEUCO3001 - 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

Efficacy of biologic drugs in short-duration versus long-duration inflammatory bowel disease: individual-patient level meta-analysis

Narrative Summary:

Crohn's disease (CD) and ulcerative colitis (UC) are inflammatory diseases often culminating in disease complications and/or the need of surgery. Biologic monoclonal antibody drugs ('Biologics') are efficacious for both diseases, but there are no systematic assessments of their efficacy if administered early after disease onset as opposed to later in the course of disease. We will analyze individual data from available clinical trials, by comparing health outcomes of patients receiving the Biologics before and after 18 months after the disease onset. The analysis will provide an important information for gastroenterologists in administering the Biologics.

Scientific Abstract:

Background: Biologic monoclonal antibody drugs (‘Biologics’) are efficacious for Crohn’s disease (CD) and ulcerative colitis (UC), but there are no systematic assessments of their efficacy if administered early after disease onset as opposed to later in the course of disease. Objective: to compare clinical response to biologics between patients with early-disease (<18months since disease onset) with patients with longer disease duration. Study Design: Electronic databases (MEDLINE, Cochrane CENTRAL register of controlled trials, the Cochrane IBD Group Specialized Trials Register, and Clinicaltrials.gov registry) were searched to identify all randomized placebo-controlled clinical trials of FDA-approved biologics for CD and UC. Individual-patient-level data (IPD) will be extracted from the identified trials through data-sharing platforms. Participants: patients included in selected trials. Main Outcome Measures: induction of remission and maintenance. Statistical Analysis: We will analyze induction of remission in patients with early-disease versus patients with longer disease duration, using a generalized linear mixed effect model, as well as by a two-stage approach using coefficient for the treatment-by-subgroup interaction within each trial.. We will perform receiver operator curve analysis of optimal disease-duration for response to biologics. All analyses will be separate for CD and UC. This first-of-its-kind meta-analysis at IPD level may elucidate the impact of early initiation of biologics, which is of paramount importance for management.

Brief Project Background and Statement of Project Significance:

Crohn's disease (CD) and ulcerative colitis (UC) are chronic immune-driven inflammatory diseases of the gut, collectively known as inflammatory bowel disease (IBD). Understanding of the progressive structural damage to the gut caused by incessant and/or recurrent bouts of inflammation in CD has led to the hypothesis that early initiation of biologic therapy (Top-down strategy) may better control underlying inflammation and prevent disease progression, compared with a later initiation of these drugs (Step-up approach) [1,2]. This contention has been supported by the SUTD trial which showed clinical benefit for top-down versus step-up treatment with infliximab in patients with CD [3]. REACT, a non-blinded controlled cluster randomized trial, did not show clinical benefit but did find lower rate of disease complications among CD patients treated by top-down compared to step-up approach [4]. However, no trial has directly compared efficacy of biologics in patients with early versus late disease. Such comparison is only available through some post-hoc sub-analyses of clinical trials and uncontrolled observations in retrospective cohorts. Some [5-7], albeit not all [8], of these studies seemed to indicate a better response rate to anti-TNF agents among CD patients with early as opposed to late-disease. Nonetheless, the impact of duration of CD on the response to biologic therapy has hitherto not been systematically investigated. Furthermore, whether such correlation exists in patients with UC has not been specifically explored.
Therefore, the primary objectives of the present study are to investigate the impact of disease duration on the rate of remission induction in CD and in UC, separately analyzed. To this end, we will compare the efficacy of FDA-approved biologics’ in patients with early short-term disease versus those with a long-duration of disease. This first-of-its-kind meta-analysis at IPD level of interaction of disease duration with the response to biologics in UC and CD may elucidate the impact of early initiation of biologics, which is of paramount importance for clinical practice and management strategies of inflammatory bowel disease.

Specific Aims of the Project:

We will analyze the following secondary endpoints in a comparative analysis of patients with short versus long-duration of disease:
- The proportion of induction of response. Clinical response is defined as CDAI reduction of 100 points from baseline for CD and as a total Mayo Drop ?30% AND ? 3 points with either bleeding score of 0 or 1 OR drop of bleeding score?1, for UC trials. When these are not available, the response is defined as per the clinical trial's designated response definition.
- The proportion of response and remission at the end of the maintenance phase of the trial (when applicable), at specific time-period between week 16-54 designated for assessment of the maintenance treatment by the trial.
- in UC patients: the proportion of colectomy for patients with short versus long-duration of disease at the end of the trial.
-- Rate of intestinal surgeries and rate of hospitalizations for patients with short versus long-duration of disease at the end of the trial.

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

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:

Electronic databases (MEDLINE, EMBASE/EMBASE classic Cochrane CENTRAL register of controlled trials, the Cochrane IBD Group Specialized Trials Register, and Clinicaltrials.gov registry) were searched to identify all randomized placebo-controlled clinical trials of FDA-approved biologics for CD and UC (by March 2016). Patients over 18 years old were included in the study. Inclusion and Exclusion criteria of these trials defined the study population. The following is the list of studies' ID in addition to those requested from YODA :
NCT00783718 (C13006)
NCT00783692 (C13007) GEMINI 2
NCT01224171 (C13011) GEMINI 3
JAPIC CTI-060298 Japan Kobayashi,
PMID 25844841 Jiang XL
NCT00032799 ENACT-1
NCT00032786 ENACT-2
NCT00078611 ENCORE
NCT00077779
NCT00445939 (M04-729)
NCT00445432 (M06-437)
NCT00055497 (M02-433)
NCT00853099 (M10-447)

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

The primary outcome in the study is induction of remission defined as remission at the end of induction as per the study-specific pre-defined timepoint and within 4-14 weeks following initiation of treatment by biologics approved by the FDA for IBD at the time of launching of this study (November 2015). A Crohn's Disease Activity Index (CDAI) <150 is defined as remission for assessment of primary outcome of CD trials, whereas a total Mayo score?2 with no individual subscore>1 is the primary remission outcome for UC trials. If these scores were unavailable, the remission/response measures are based on the specific clinical score and outcome definition employed by the respective clinical trial.

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

Biologics treatment in interaction with duration of disease (before and after 18 months from the disease onset).

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

Exposure to prior anti-TNF, use of concomitant immunomodulators, prior surgery, disease phenotype and extent for CD, disease extent for UC, age, gender, BMI, smoking status, CRP (elevated or not at baseline as per the laboratory normal range in the respective trial), albumin (below normal or not), difference in clinical scores used to measure the efficacy outcomes, and the class of the biologic (anti-TNF vs. anti-integrins)

Statistical Analysis Plan:

Secondary analyses include analyses of the response to induction, the maintenance of response, maintenance of remission, and the proportion of colectomy (for UC patients only), as well as the sub-group analysis of the primary outcome within the strata of patients treated with anti-TNF class of drugs and patients treated by anti-integrins.
Pre-planned sensitivity analyses will assess the primary outcome by:
1) including also trials with high risk of bias;
2) including only the studies employing the pre-defined clinical score criterion for remission induction (CDAI<150 or Mayo?2 with no individual subscore>1 for CD and UC, respectively);
3) Using a fixed-effect model to pool data if heterogeneity assessment reveals I2 <50%;

4) including only trials in which all patients were anti-TNF naïve;
5) including only patients who rolled over to the maintenance phase after responding to induction (only for the outcome of maintenance of remission, in applicable trials)
6) analyzing the primary outcomes using techniques of Bayesian analysis with vague priors for the treatment effect estimates.
7) analyzing the primary outcomes separately for industry and academic sources.
To assess the optimal threshold for duration of disease that best "predicts" the likelihood of patients' response to treatment, a summary Receiver Operator Characteristics (ROC) curve will be constructed based on the random effects generalized linear model adjusting for clustered structure of the pooled database, with the study outcomes as outlined above and continuous disease duration as independent covariate in the model.
SAS 9.4 and R (studio) software will be used for the main statistical analysis. We will generate Forest plots of pooled effect estimates (RR or OR) with 95% CIs, as well as funnel plots. The latter are assessed for evidence of asymmetry and therefore possible publication bias or other small study effects, using the Egger test, if there are sufficient (n=10) eligible studies included in the meta-analysis, in line with published recommendations [35].

Due to character limits, please see supplemental attachment for additional methods performed (sections "General approach in meta-anal" and "Specific analyses .
Software Used:
I am not analyzing participant-level data / I will not be using these software for analyses in the secure platform

Project Timeline:

We will analyze the data within 6 months after data become available to the researchers. Most of the analysis has been performed in the YODA trails platform, separately from other companies' trials. The analysis included data cleaning, variables definitions and a meta-analysis based on the separate YODA trials.
The proposed analysis will be conducted within the Vivli platform. Full approval for #2019-4107 will be contingent upon closing out #2015-0677. We would like the datasets derived under #2015-0677 (or at least the sascodes used by us for creating those datasets) be made available to us under #2019-4107, to save months of work while cleaning and defining the working variables. Upon completion of analyses we will summarize the findings in a manuscript (additional 2-3 months) and submit for publication.

Dissemination Plan:

Findings will be published in a peer-reviewed journal and disseminated via presentations at scientific meetings and links with patients groups and organizations. BMJ is one of the optional journals for publication.

Bibliography:

1. Peyrin-Biroulet L, Billioud V, D'Haens G, Panaccione R, Feagan B, Panés J, Danese S, Schreiber S, Ogata H, Hibi T, Higgins PD, Beaugerie L, Chowers Y, Louis E, Steinwurz F, Reinisch W, Rutgeerts P, Colombel JF, Travis S, Sandborn WJ. 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; 107:1770-6
2. D'Haens GR, Panaccione R, Higgins PD, Vermeire S, Gassull M, Chowers Y, Hanauer SB, Herfarth H, Hommes DW, Kamm M, Löfberg R, Quary A, Sands B, Sood A, Watermeyer G, Lashner B, Lémann M, Plevy S, Reinisch W, Schreiber S, Siegel C, Targan S, Watanabe M, Feagan B, Sandborn WJ, Colombel JF, Travis S. The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organization: when to start, when to stop, which drug to choose, and how to predict response? Am J Gastroenterol 2011; 106:199-212
3. D'Haens G, Baert F, van Assche G, Caenepeel P, Vergauwe P, Tuynman H, De Vos M, van Deventer S, Stitt L, Donner A, Vermeire S, Van de Mierop FJ, Coche JC, van der Woude J, Ochsenkühn T, van Bodegraven AA, Van Hootegem PP, Lambrecht GL, Mana F, Rutgeerts P, Feagan BG, Hommes D; Belgian Inflammatory Bowel Disease Research Group; North-Holland Gut Club. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial Lancet. 2008 Feb 23;371(9613):660-7
4. Khanna R, Bressler B, Levesque BG, Zou G, Stitt LW, Greenberg GR, Panaccione R, Bitton A, Paré P, Vermeire S, D'Haens G, MacIntosh D, Sandborn WJ, Donner A, Vandervoort MK, Morris JC, Feagan BG. Early combined immunosuppression for the management of Crohn's disease (REACT): a cluster randomised controlled trial. Lancet 2015 ;386:1825-34
5. Schreiber S, Colombel JF, Bloomfield R 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; 105:1574-82

6. Schreiber S, Reinisch W, Colombel JF 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;7:213-21
7. Ma C, Beilman CL, Huang VW et al. Anti-TNF Therapy Within 2 Years of Crohn's Disease Diagnosis Improves Patient Outcomes: A Retrospective Cohort Study. Inflamm Bowel Dis 2016; 22:870-9
8. Kotze PG, Ludvig JC, Teixeira FV et al. Disease duration did not influence the rates of loss of efficacy of the anti-TNF therapy in Latin American Crohn's disease patients. Digestion. 2015;91(2):158-63.
9. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0. http://handbook.cochrane.org/. Accessed 17 Oct 2015
10. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62(10):1006–1012
11. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic reviews. 2015;4:1. doi: 10.1186/2046-4053-4-1
12. Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, Lichtiger S, D'Haens G, Diamond RH, Broussard DL, Tang KL, van der Woude CJ, Rutgeerts P; SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. 2010 Apr 15;362(15):1383-95
13. Schreiber S, Colombel JF, Bloomfield R, Nikolaus S, Schölmerich J, Panés J, Sandborn WJ; PRECiSE 2 Study Investigators. 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 Jul;105(7):1574-82
14. 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 Jul;105(7):1583-5
15. Schreiber S, Reinisch W, Colombel JF, Sandborn WJ, Hommes DW, Robinson AM, Huang B, Lomax KG, Pollack PF. 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 Apr;7(3):213-21
16. Nuij V, Fuhler GM, Edel AJ, Ouwendijk RJ, Rijk MC, Beukers R, Quispel R, van Tilburg AJ, Tang TJ, Smalbraak H, Bruin KF, Lindenburg F, Peyrin-Biroulet L, van der Woude CJ; Dutch Delta IBD Group. Benefit of Earlier Anti-TNF Treatment on IBD Disease Complications? J Crohns Colitis. 2015 Nov;9(11):997-1003
17. Safroneeva E, Vavricka SR, Fournier N, Pittet V, Peyrin-Biroulet L, Straumann A, Rogler G, Schoepfer AM; Swiss IBD Cohort Study Group. Impact of the early use of immunomodulators or TNF antagonists on bowel damage and surgery in Crohn's disease . Aliment Pharmacol Ther. 2015 Oct;42(8):977-89
18. Oussalah A, Evesque L, Laharie D, Roblin X, Boschetti G, Nancey S, Filippi J, Flourié B, Hebuterne X, Bigard MA, Peyrin-Biroulet L. A multicenter experience with infliximab for ulcerative colitis: outcomes and predictors of response, optimization, colectomy, and hospitalization. Am J Gastroenterol. 2010 Dec;105(12):2617-25
19. Matsumoto T, Iida M, Motoya S, Haruma K, Suzuki Y, Kobayashi K, Ito H, Miyata M, Kusunoki M, Chiba T, Yamamoto S, Hibi T. Therapeutic efficacy of infliximab on patients with short duration of Crohn's disease: a Japanese multicenter survey. Dis Colon Rectum. 2008 Jun;51(6):916-23
20. Peyrin-Biroulet L, Billioud V, D'Haens G, Panaccione R, Feagan B, Panés J, Danese S, Schreiber S, Ogata H, Hibi T, Higgins PD, Beaugerie L, Chowers Y, Louis E, Steinwurz F, Reinisch W, Rutgeerts P, Colombel JF, Travis S, Sandborn WJ. 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.
21. Bickston SJ, Behm BW, Tsoulis DJ, Cheng J, MacDonald JK, Khanna R, Feagan BG. Vedolizumab for induction and maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev 2014, CD007571
22. MacDonald JK, McDonald JW. Natalizumab for induction of remission in Crohn's disease. Cochrane Database Syst Rev 2007, CD006097
23. Behm BW, Bickston SJ. Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev 2008 CD006893
24. Lawson MM, Thomas AG, Akobeng AK. Tumour necrosis factor alpha blocking agents for induction of remission in ulcerative colitis Cochrane Database Syst Rev 2006 CD005112
25. Dassopoulos T, Sultan S, Falck-Ytter YT, Inadomi JM, Hanauer SB. American Gastroenterological Association Institute technical review on the use of thiopurines, methotrexate, and anti-TNF-? biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. Gastroenterology 2013; 145(6):1464-78
26. Dignass A, Lindsay JO, Sturm A, Windsor A, Colombel JF, Allez M, D'Haens G, D'Hoore A, Mantzaris G, Novacek G, Oresland T, Reinisch W, Sans M, Stange E, Vermeire S, Travis S, Van Assche G. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. J Crohns Colitis 2012; 6(10):991-1030,
27. Dignass A, Van Assche G, Lindsay JO, Lémann M, Söderholm J, Colombel JF, Danese S, D'Hoore A, Gassull

M, Gomollón F, Hommes DW, Michetti P, O'Morain C, Oresland T, Windsor A, Stange EF, Travis SP; European Crohn's and Colitis Organisation (ECCO]. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: current management. J Crohns Colitis. 2010 Feb;4(1):28-62.
28. Higgins JPT et al, Cochrane handbook for systematic reviews of interventions: version 5.0.0, 2008
29. Guyatt GH, Oxman AD, Montori V, Vist G, et al. GRADE guidelines: 5. Rating the quality of evidence – Publication bias. J Clin Epidemiol 2011; 64:1277-1282
30. Thompson SG, Higgins JPT. Can meta-analysis help target interventions at individuals most likely to benefit?. Lancet 2005; 365:341-346
31. Tierney JF, Vale C, Riley R, Smith CT, Stewart L, Clarke M, Rovers M. Individual Participant Data (IPD) Meta-analyses of Randomized Controlled Trials: Guidance on Their Use. PLoS Med 2015; 12(7): e1001855.
32. Riley RD, Lambert PC, Staessen JA, Wang J, Gueyffier F, Thijs L, Boutitie F. Meta-analysis of continuous outcomes combining individual patient data and aggregate data. Stat Med 2008; 27(11):1870-93
33. Debray TP, Moons KG, van Valkenhoef G, Efthimiou O, Hummel N, Groenwold RH,Reitsma JB; GetReal Methods Review Group. Get real in individual participant data (IPD) meta-analysis: a review of the methodology. Res Synth Methods 2015; 6(4):293-309.
34. Simmonds MC, Higgins JP. Covariate heterogeneity in meta-analysis: criteria for deciding between meta-regression and individual patient data. Stat Med 2007; 26(15):2982-99
35. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60
36. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7:177-88

Supplementary Material:

https://yoda.yale.edu/sites/default/files/protocol_manuscript_r1.docx
https://yoda.yale.edu/sites/default/files/cod_by_sbh.pdf
https://yoda.yale.edu/sites/default/files/summary.docx
https://yoda.yale.edu/sites/default/files/dua_extension_letter2020-signed_fe.pdf
https://yoda.yale.edu/sites/default/files/details_to_be_added_to_the_stats_methods_in_the_protocol.docx