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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

http://yoda.yale.edu/system/files/disclosure_form_ac_de_vries.pdf
http://yoda.yale.edu/system/files/disclosure_form_cj_van_der_woude.pdf
http://yoda.yale.edu/system/files/disclosure_form_d_nieboer_0.pdf
http://yoda.yale.edu/system/files/disclosure_form_emj_beelen_0.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. 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

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

Research Proposal

Project Title

Thiopurines versus anti-TNFa for the prevention of postoperative recurrence in Crohn's disease – a meta-analysis of individual patient data

Narrative Summary:

Current ECCO and AGA guidelines do not express a preference for azathioprine or anti-TNFa in the prevention of postoperative recurrence in CD patients. Individual patient data analysis of available randomized controlled trials would be valuable to be able to account for confounding factors and risk factors. This could help provide a reliable advice in postoperative CD treatment strategy. Therefore the aim of this study is to perform a meta-analysis of individual patient data of randomized controlled trials on thiopurines or anti-TNFa for the prevention of postoperative CD recurrence.

Scientific Abstract:

Background
Current ECCO and AGA guidelines advice to start prophylactic postoperative medication in CD patients at high risk of recurrence. Both guidelines do not express a preference for one of both therapies in postoperative CD patients.
Objective
The aim of this study is to perform a meta-analysis of individual patient data of randomized controlled trials on thiopurines or anti-TNFa for the prevention of postoperative CD recurrence.
Study design
Meta-analysis of individual participant data
Partcipants
Randomized controlled trials on thiopurines or anti-TNFa monotherapy for the prevention of endoscopic and/or clinical postoperative recurrence in adult CD patients after ileocolic resection will be included.
Main outcome measures:
Primary outcome: Postoperative endoscopic recurrence, defined as Rutgeerts ? i2
Secondary outcomes: Postoperative clinical recurrence, defined as CDAI >200 or HBI ?8
Statistical analysis:
A network meta-analysis will be performed. Individual patient data will be used for kaplan meier analysis and cox regression analysis to adjust for known confounders and study protocols. Patients will be stratified in high or low risk categories.

Brief Project Background and Statement of Project Significance:

Postoperative recurrence after ileocolonic resection in Crohn's disease (CD) patients is common and is typically

divided in clinical, endoscopic and surgical recurrence. Previous reports show that endoscopic recurrence occurs in 65-80% of patients, whereas symptomatic clinical recurrence occurs in 20-25% of patients within 1 year. Up to 50% of CD patients will need additional intestinal surgery within 20 years. (1-4) Ileocolonoscopy is considered the gold standard in diagnosis of postoperative recurrence, for the identification of presence and severity of recurrence and prediction of the clinical disease course. (5)

Anti-TNFa has proven to be effective in the prevention of postoperative recurrence in CD. A trial by Regueiro et al. showed that a smaller proportion of patients on infliximab had endoscopic recurrence compared to placebo after 76 weeks, with recurrence rates of 30.6% vs 60.0% respectively. Clinical recurrence rate did not differ significantly between groups. (6) The effectiveness of thiopurines in the prevention of postoperative recurrence has also been studied. Mowat et al. found that mercaptopurine is effective in preventing postoperative recurrence, but only in smokers. (7) Another study showed that patients treated with a combination of azathioprine and metronidazole had less severe recurrences after 1 year. (8) Studies comparing the efficacy of thiopurines and anti-TNFa in postoperative setting are scarce difficult to compare because of the inclusion of heterogeneous populations (high- and low risk), differences in follow-up time, in previous IBD medication and in outcome definitions. (9-11) Current ECCO and AGA guidelines advice to start prophylactic postoperative medication in CD patients at high risk of recurrence. Both guidelines do not express a preference for one of both therapies in postoperative CD patients. (5, 12) Individual patient data analysis of available randomized controlled trials would be highly valuable to be able to account for confounding factors and risk factors. This could help provide a reliable advice in postoperative CD treatment strategy. Therefore the aim of this study is to perform a meta-analysis of individual patient data of randomized controlled trials on thiopurines or anti-TNFa for the prevention of postoperative CD recurrence.

Specific Aims of the Project:

The aim of this study is to perform a meta-analysis of individual patient data of randomized controlled trials on thiopurines or anti-TNFa for the prevention of postoperative CD recurrence.

What is the purpose of the analysis being proposed? Please select all that apply.

Participant-level data meta-analysisParticipant-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:

A systematic search will be performed in Embase, Medline, Web of science, the Cochrane database and Google scholar. Randomized controlled trials on thiopurines or anti-TNFa monotherapy for the prevention of endoscopic and/or clinical postoperative recurrence in adult CD patients after ileocolic resection will be included. Conference abstracts and studies that are unavailable in the English language will be excluded. Search terms include Crohn's disease, anti-TNFa (infliximab, adalimumab) thiopurines (mercaptopurine, azathioprine) and postoperative recurrence. Retrieved studies will be independently assessed by two individual researchers. Disagreements will be resolved by consensus.

Data will be pooled according to the prescribed therapies. (thiopurines or anti-TNFa) Other included data are the raw data from from the following scientific publications:
- Ardizzone et al. Gastroenterology. 2004
- Armuzzi et al. JCC. 2013
- Lopez-Sanroman et al. JCC. 2017
- Mowat et al. Lancet Gastroenterol Hepatol. 2016
- Savarino et al. Am J gastroenterol. 2013

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

Primary outcome: Postoperative endoscopic recurrence, defined as Rutgeerts ? i2
Secondary outcomes: Postoperative clinical recurrence, defined as CDAI >200 or HBI ?8

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

Anti-TNFa or thiopurine started postoperatively for the prevention of recurrence of Crohn's disease

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

your study:

High risk of postoperative recurrence will be defined according to guidelines, (5, 12) by one or more of the following risk factors: active smoking, penetrating disease behaviour and previous bowel surgery.

Possible associated factors for postoperative recurrence used in analysis for confounders are: Time between CD diagnosis and surgery, previous medication used, previous surgery, disease behaviour, smoking status, length of the resected segment, time between surgery and start of postoperative medication.

Statistical Analysis Plan:

Descriptive statistics will be applied for baseline characteristics of the cohorts. Categorical variables will be described using frequencies and percentages and compared between groups using Chi square test. Continuous variables will be described using mean and standard deviation or median and interquartile range for non-normally distributed variables. Comparison between groups of continuous variables will be done using the t-test or Mann-Whitney U test. A network meta-analysis will be performed with pooled data. For individual participant data, Kaplan meier analysis will be applied to determine endoscopic recurrence and clinical recurrence incidences and time-to-recurrence. Patients will be stratified in high or low risk category and different treatments will be compared using cox regression analysis where we adjust for known confounders and study procotols. Results will be expressed as hazard ratio's (HR) with 95% confidence intervals.

Project Timeline:

Anticipated start date: June 2018. Analysis completion date: August/September 2018. Drafted manuscript: December 2018. Anticipated date results reported back to the Yoda project: March 2019

Dissemination Plan:

Results of this study will be presented for publication as a manuscript to a scientific journal. Anticipated target journal is Gut.

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Supplementary Material:

protocol_ipd-ma_thiopurines_vs_anti-tnfa_for_the_prevention_of_postoperative_recurrence.pdf