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

Study protocol

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Backgrounds

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-TNFα 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-TNFα 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-TNFα for the prevention of postoperative CD recurrence.
Methods

Search
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-TNFα 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-TNFα (infliximab, adalimumab) thiopurines (mercaptopurine, azathioprine) and postoperative recurrence. Retrieved studies will be independently assessed by two individual researchers. Disagreements will be resolved by consensus. Authors of the selected randomized controlled trials will be contacted for data sharing. A data sharing agreement will be set up after which the (anonymized) data will be requested.

Analysis

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

Risk stratification and confounding factors
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
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. 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 protocols. Results will be expressed as hazard ratio’s (HR) with 95% confidence intervals.
References