THE EFFICACY OF POST OPERATIVE PROFILAXIS WITH EITHER VEDOLIZUMAB OR USTEKINUMAB FOR CROHN'S DISEASE

STUDY PROTOCOL

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INTRODUCTION

Despite the introduction of several targeted biologics for Crohn's disease (CD) many patients still require surgical intervention while ileocecal resection is the most common procedure[1]. Clinical and endoscopic recurrence are common following surgery with 70% of the patients demonstrating endoscopic lesions in the neo-terminal ileum at one year following resection and substantial proportion of patients require repeated surgeries[1]. Postoperative treatment with imidazoles and thiopurines have shown modest reduction in disease recurrence rates at 1 year[2, 3], while using an anti TNF rates of endoscopic recurrence within one year ranges between 10-35% [4-7]. Moreover, based on indirect comparisons, anti TNF therapies are considered the most effective treatment strategies for the prevention of postoperative recurrence[8].

In recent years, new biologic therapies for CD have emerged. These include vedolizumab, a gut selective anti-integrin antibody and ustekinumab, anti IL12/IL23 antibody, both used to treat patients with moderate to severe disease. Clinical trials have demonstrated their efficacy in inducing and maintaining clinical and endoscopic remission in both anti TNF naïve and experienced patients[9-11]. Little is known about their efficacy in preventing postoperative disease recurrence as these drugs have not yet received regulatory approval for this indication. Still these therapies are used off label for post-operative prophylaxis. Yamada et al have recently reported a single center real-world experience with vedolizumab treatment for the prevention of disease recurrence, which showed that the clinical and biologic remission rates at 6-12 months postoperative were similar with vedolizumab and anti TNF. However, on multivariate and propensity score-matched analyses, endoscopic remission rates were lower in patients treated with vedolizumab[12].

In this multicenter, real-world study, we aim to evaluate the efficacy of either vedolizumab or ustekinumab in achieving prolonged clinical, endoscopic and biologic remission after surgery and to compare their efficacy to anti TNFs.

HYPOTHESIS

Post-operative prophylaxis with vedolizumab or ustekinumab is expected to result in an endoscopic recurrence rate of 35 % within 12 months after curative surgery.

DESIGN AND OBJECTIVE(S)

A multicenter retrospective cohort study to assess the efficacy of either vedolizumab or ustekinumab (cases) compared with anti-TNFs (controls) for the prevention of CD recurrence after a curative ileocecal resection.

Study population

Adults (>17 years of age) with established CD, who underwent a curative ileocecal resection between 2015-2018, and were assigned a prophylaxis regiment within 6 months of surgery, with a follow-up ileocolonoscopy after prophylaxis and of at least 12 months post-op follow-up.

Study endpoints

Primary endpoint

Endoscopic recurrence rates within 12 months after a curative ileocecal resection

Secondary endpoints

- Endoscopic recurrence rates in 24, and 36-months after surgery.
- Clinical and biochemical recurrence rates within 12, 24, and 36-months after surgery
- Recurrent surgical rates within 12, 24, and 36-months after surgery
- Safety and side effects

Endpoints, co-variates and variables

- Endoscopic recurrence- a Rutgeert's score ≥ i2 (appendix 1) or colonic segmental SES-CD≥6 (appendix 2) and/or any new stricture
- Endoscopic stricture- per colonoscopy or imaging if available
- Clinical recurrence - Harvey-Bradshaw index (HBI) > 4 (appendix 3).
- Biological recurrence - C-reactive protein (CRP) > 10 mg/L or fecal calprotectin > 150 microgram/gram stool
- Time to treatment change
- Time to treatment dose escalation
- Time to initiate steroids

A comprehensive chart review will be conducted and the following data will be extracted:

Before surgery

- Patient demographics
- Smoking history
- Comorbidities: immune mediated diseases, any cancer, infectious disease

- Disease phenotype – Montreal classification – ALB at the time of surgery (before operation) (appendix 4)
- Perianal disease
- Extraintestinal manifestation
- History of exposure to IBD related medications (response/ failures, side effects, tolerability)
- Indications for surgery
- Perioperative medications
- CD surgery information and early post-operative complications
- Reasons for electing a specific post-operative prophylaxis strategy

<u>After surgery and at prophylaxis</u>

- Post-operative endoscopic recurrence Rutgeert's score at anastomosis or SES-CD at every endoscopy after prophylaxis
- CTE/MRE/capsule endoscopy/IUS if performed
- HBI/PGA
- CRP/ fecal calprotectin
- Steroid use within 12-months
- Prophylactic drug dosing within follow-up
- For anti-TNFs – therapeutic drug monitoring data
- Immunomodulatory usage
- IBD related hospitalisations
- Adverse events

<u>Inclusion criteria</u>

- Established diagnosis of CD
- Ileocecal resection (including re-do-"ileocecal" resection)
- Adult>17 years old at the time of surgery
- Initiation of prophylaxis treatment with ustekinumab/ vedolizumab or anti TNF/ within 6 months after surgery
- At least one ileocolonoscopy after initiating prophylaxis therapy
- At least 12 months post-op follow-up
- Concomitant immunomodulators, mesalamine or azoles therapy is allowed
-

<u>Exclusion criteria</u>

- Inflammation at remote sites outside the resected area including active perianal disease
- Total or subtotal proctocolectomy
- Any small bowel resection other than curative ileocecectomy
- Large bowel resection (segmental, subtotal, total)
- Pregnancy during the first year after surgery

There is no restriction for inclusion based on prior treatment. Prior treatment should be recorded including- exposure time, concomitant treatment, drug and anti-drug antibodies if available. There is no restriction for post-operative concomitant treatment. This treatment should be recorded including- date of initiation, dosage, discontinuation date.

STATISTICAL ANALYSIS

Descriptive analysis of patients' characteristics will be presented by using percentages for categorical variables and median and interquartile range for continuous variables. Differences in the means between subgroups will be compared using Mann-Whitney U test. Comparisons between categorical variables will be analysed using the Fisher's exact test. The hazard ratios for disease recurrence rates after surgery for each prophylaxis strategy (anti TNFs, vedolizumab or ustekinumab) will be analysed by Cox regression. Comparison between groups will be based on multivariate analysis.

Sample size was determined assuming a 20% recurrence for patients under anti TNFs in the first year and a 35% recurrence in either vedolizumab or ustekinumab groups[13]. We also took into account the fact that most patients are treated for prophylaxis with anti TNFs and the fact that vedolizumab is available in the market from 2015 and ustekinumab only from 2017 (allowing only 12-months of post-surgical follow-up for the ustekinumab group). Comparison between cases (vedolizumab or ustekinumab) and controls (anti TNFs) will be based on a ratio 1:3-4. Based on these assumptions we will require a total of 250 patients treated with anti TNFs, 84 patients treated with vedolizumab and 51 patients treated with ustekinumab to achieve 80% power at 0.05 significance level.

ETHICAL CONSIDERATIONS

This a retrospective study, ethics should follow the local IRB requirements considering exempting participants from signing an informed consent form.

Appendix 1

Rutgeert's score

Endoscopic findings	Score
No aphthous ulcers	0
Less than five aphthous ulcers	1
More than five aphthous lesions with normal intervening mucosa, skip areas of larger lesions or lesions confined to ileocolonic anastomosis (ie, less than 1 cm in length)	2
Diffuse aphthous ileitis with diffusely inflamed mucosa	3
Diffuse inflammation with larger ulcers, nodules and/or narrowing	4

Appendix 2

The Simple Endoscopic Score for Crohn Disease (SES-CD)

Variable	0	1	2	3
Presence of ulcers	None	Aphthous ulcers 0.1–0.5 cm	Large ulcers 0.5–2 cm	Very large ulcers >2 cm
Ulcerated surface	None	<10%	10–30%	>30%
Affected surface	Unaffected segment	<50%	50–75%	>75%
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

	Ileum	Right colon	Transverse colon	Left colon	Rectum	Total
Presence of ulcers 0–3						
Ulcerated surface 0–3						
Affected surface 0–3						
Presence of narrowings 0–3						
					*SES-CD=	

Appendix 3

Harvey-Bradshaw Index (HBI)

General well-being (yesterday)

□Very well □Slightly below par □Poor □Very poor □Terrible

Abdominal pain (yesterday)

□None □Mild □Moderate □Severe

Number of liquid or soft stools per day (yesterday)

□0 □1 □2 □3 □4 □5 □6 □7 □8 □>8

Abdominal mass

□None □Dubious □Definite □Definite and tender

Complications (check all that apply)

□Arthralgia □Uveitis □Erythema nodosum □Aphthous ulcers

□Pyoderma gangrenosum □Anal fissure □New fistula □Abscess

Appendix 4

Montreal classification

Age at diagnosis	A1 below 16 year
	A2 between 17 and 40 year
	A3 above 40 year
Location	L1 ileal
	L2 colonic
	L3 ileocolonic
	L4 isolated upper disease*
Behavior	B1 non-stricturing, non-penetrating
	B2 stricturing
	B3 penetrating
	p perianal disease modifier†

*L4 is a modifier that can be added to L1–L3 when co

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