A SINGLE CENTER OPEN LABEL PROSPECTIVE STUDY OF ORAL TOFACITINIB IN PATIENTS WITH CHRONIC POUCHITIS

Gil Y. Melmed, MD, MS

F. Widjaja Foundation Inflammatory Bowel and Immunobiology Research Institute

Inflammatory Bowel Disease Center

Cedars-Sinai Medical Center

Los Angeles, CA 90048

NCT: NCT04580277

Document Date: 02 August 2022

Contents

Background

Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is currently the standard surgical treatment for patients with ulcerative colitis (UC), with approximately 30% of patients with UC requiring IPAA for medically refractory disease or colorectal neoplasia. Pouchitis is an idiopathic inflammatory disease of the ileal pouch and is the most common long-term complication in subjects with IPAA, resulting in patient morbidity, missed work and school, and diminished quality of life. Studies with long follow up duration suggest that up to 80% of patients with IPAA will experience at least one episode of pouchitis in their lifetime[1,2]. While most patients with pouchitis respond well to short courses of antibiotic therapy, about 10-20% of patients develop a chronic antibiotic-dependent or antibiotic-refractory course of pouchitis [3,4]. Chronic pouchitis is associated with significant morbidity, poor quality of life and is a risk factor for pouch failure[5,6].

There are currently no licensed treatments for chronic pouchitis and the current treatment is largely empiric or guided by low-quality evidence from case series and small observational studies. Chronic antibiotic therapy is a potential treatment option only for patients with chronic antibiotic dependent pouchitis (CADP) though it is associated with risk of antibiotic related side effects and emergence of multi-drug resistant organisms[7,8]. Other commonly used treatments for chronic pouchitis are ileal release budesonide and biologic drugs. Ileal release budesonide is effective in 58-75% patients with chronic pouchitis but its chronic use is associated with long-term corticosteroid-associated side effects and is generally discouraged[9,10]. Anti-tumor necrosis factor (anti-TNF) agents are widely used for treatment of chronic pouchitis though a recent meta-analysis found these medications to be only modestly effective with remission rates of 10% and 37% in short-term and long-term, respectively, in patients with chronic antibiotic-refractory pouchitis (CARP)[11]. A few recent observational studies suggest that vedolizumab and ustekinumab could also be effective in chronic pouchitis but the remission rates with these drugs also remain low[12,13]. Hence, given the availability of limited treatment options in chronic pouchitis and their modest efficacy, there is a significant unmet need for additional effective medical therapies in these patients. This treatment gap is likely to worsen in the future as the population of patients who undergo IPAA surgery for UC increases with time.

Janus kinases (JAKs) play a central role in transmitting the pro-inflammatory effects of multiple cytokines that result in chronic inflammation in inflammatory bowel diseases[14]. Targeting the JAK-STAT pathway is an effective therapeutic approach in inflammatory bowel diseases (IBD). Tofacitinib, an oral small molecule JAK inhibitor is effective and safe for treatment of ulcerative colitis[15]. JAK-STAT pathway might also have a potential role in the pathogenesis of chronic pouchitis. In a study of thirty-six patients who underwent IPAA surgery for UC, patients who

develop pouchitis were noted to have increased levels of STAT1alpha as well as STAT1beta expression and activation in comparison with both normal pouch and normal ileal mucosa. In addition, improvement of pouchitis after treatment with antibiotics was associated with normalization of STAT1 expression and activation[16]. These findings suggest that activation of STAT1 correlates with pouchitis disease activity. Currently, there is no data on the efficacy of JAK inhibitors in treatment of chronic pouchitis. However, similarities in the pattern of activation of STAT1 in pouchitis and ulcerative colitis may suggest a common pathway in the immunobiology of both diseases and a potential role for JAK inhibitors like tofacitinib in treatment of chronic pouchitis.

Aims and Objectives

This study is designed to evaluate the efficacy and safety of oral tofacitinib in subjects with chronic pouchitis and its impact in health-related quality of life. Chronic pouchitis is defined by a modified pouchitis disease activity index (mPDAI) score ≥5 and a minimum endoscopic sub-score of 2 (outside the staple or suture line) AND one of the following:

- ≥3 recurrent episodes of pouchitis within 1 year prior to the screening visit treated with ≥2 weeks of antibiotic or other prescription therapy.
- Requiring maintenance antibiotic therapy taken continuously for ≥4 weeks immediately prior to the baseline study visit.
- No response to >=4 weeks of antibiotic therapy.

Objective 1: Assess the efficacy of tofacitinib in patients with chronic pouchitis.

Hypothesis: Tofacitinib is effective in reducing clinical symptoms (modified pouchitis disease activity index), inflammatory biomarkers (fecal calprotectin), and endoscopic appearance among patients with chronic pouchitis.

Objective 2: Assess the safety of tofacitinib in patients with chronic pouchitis

Hypothesis: Tofacitinib is safe and well tolerated in patients with chronic pouchitis

Objective 3: Determine the effect of oral tofacitinib on health-related quality of life in patients with chronic pouchitis.

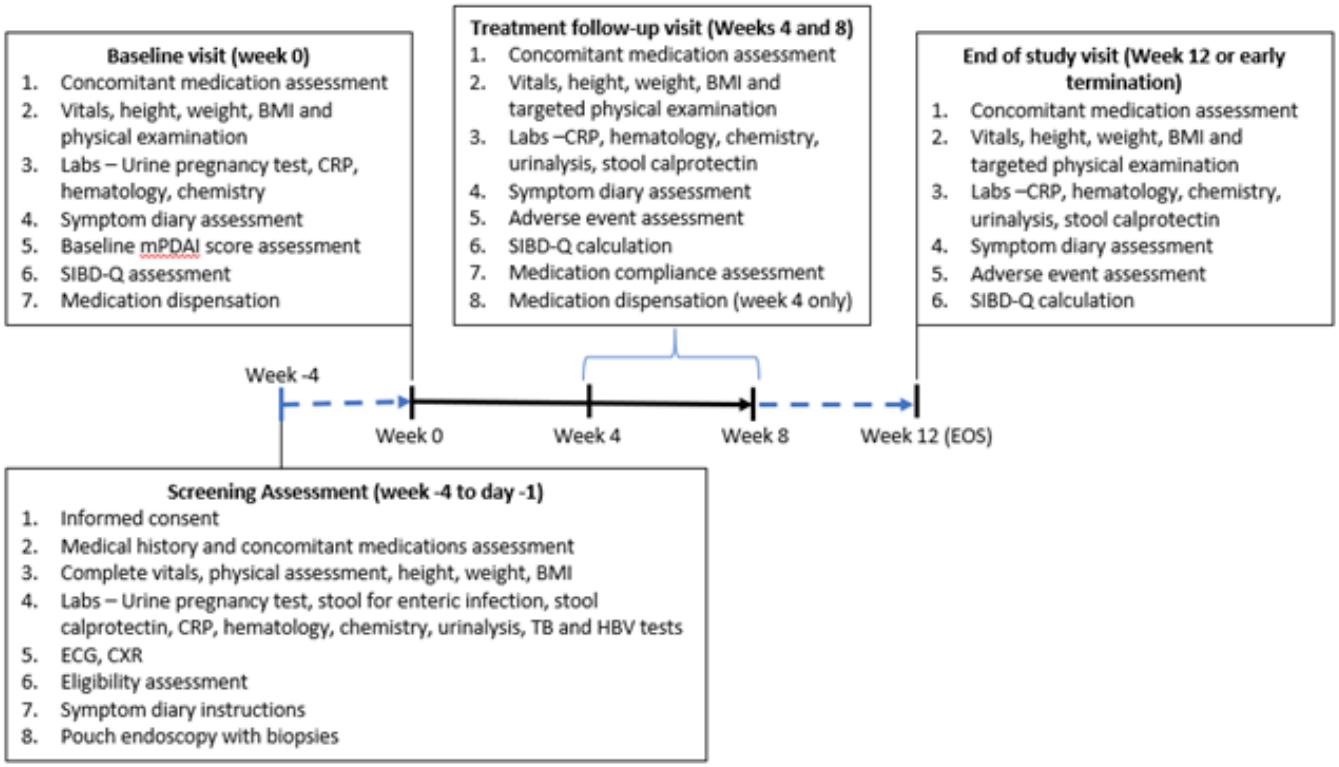
Hypothesis: Tofacitinib treatment is associated with improved HRQOL in patients with chronic pouchitis

Study Design and Methods

Overview of Study Design

The proposed study is a phase 2, open-label study of tofactinib in treatment of patients with chronic pouchitis. Patients with chronic active pouchitis will be recruited from the Cedars-Sinai Inflammatory Bowel Disease Center. The total expected duration of participation is 16 weeks including a 4-week screening period, 8 weeks of tofacitinib therapy and an end of study visit 4 weeks after completion of 8-week tofacitinib treatment. Subjects experiencing early withdrawal from study will be scheduled for a safety follow-up visit 4 weeks after the date of withdrawal. The primary outcome is a reduction in the mPDAI score ≥2 at week 8 compared to baseline. We will also assess secondary outcomes including changes in clinical symptoms, fecal calprotectin, HRQOL, and mucosal appearance.

Figure 1: Study Design



Study Population

The study will be open to adult patients (ages 18-80 years) seen at the Cedars-Sinai Inflammatory Bowel Disease Center who meet eligibility criteria.

Inclusion criteria

1. Male or female subjects ages 18 to 80

2. Subjects with a history of proctocolectomy with ileal pouch anal anastomosis (IPAA) for UC at least 6 months prior to screening.
3. Subjects with pouchitis that is chronic, defined by a mPDAI score ≥5 assessed as the average from 3 days immediately prior to the baseline study visit and a minimum endoscopic sub-score of 2 (outside the staple or suture line) with either (a) ≥ 3 recurrent episodes within 1 year prior to the screening treated with ≥2 weeks of antibiotic or other prescription therapy, (b) requiring maintenance antibiotic therapy taken continuously for ≥4 weeks immediately prior to the baseline study visit, or (c) not responding to >=4 weeks of antibiotic therapy.
4. Women of childbearing potential must have documentation of a negative pregnancy test at screening and must agree to use two highly effective methods of birth control during the study and for at least 1 month after completion of study drug dosing.
5. Subjects willing and able to give informed consent.

Exclusion criteria

1. Subjects with IPAA surgery done for Crohn's disease (CD) or familial adenomatous polyposis (FAP) indications.
2. Subjects with CD-like complications including non-anastomotic strictures and active perianal fistulae, isolated or predominant cuffitis or mechanical complications of the ileal pouch.
3. Surgical complications such as anal stenosis, anastomotic leak, or fistula.
4. Subjects with prior exposure to tofacitinib.
5. Subjects with impending need for surgery.
6. Subjects with a diverting stoma.
7. Subjects with a prior history or risk factors for venous thromboembolism.
8. Subjects with active bacterial, parasitic, fungal, mycobacterial, or viral infection (including C. difficile and GI infections observed upon stool testing at screening), any infection requiring hospitalization or intravenous antibiotics within 3 months prior to screening, any infection requiring oral antimicrobial treatment within 2 weeks prior to screening.
9. Subjects with a history of latent or active tuberculosis or a positive QuantiFERON®-TB Gold result.
10. Subjects positive for hepatitis B virus (HBV) surface antigen, hepatitis B virus core antibody with a negative hepatitis B surface antibody or with detectable serum hepatitis B DNA.
11. Female subjects who are pregnant, lactating, breastfeeding or planning to become pregnant during the study or within 1 month after the last dose of study drug.
12. Female subjects of childbearing potential who are sexually active with non-sterilized male partners and do not agree to using two highly effective methods of contraception from signing of informed consent throughout the duration of the study and for 4 weeks after the last dose.
13. Subjects with clinically significant laboratory abnormalities at study screening including: AST or ALT ≥ 3x the upper limit of normal, alkaline phosphatase ≥ 2x the upper limit of normal,

total bilirubin ≥ 2 mg/dL (unless confirmed diagnosis of Gilbert's), estimated creatinine clearance < 60 mL/min , total white blood cell count (WBC) < 3 x 10^9/L, absolute neutrophil count < 1.3 x 10^9/L, absolute lymphocyte count < 0.5 x 10^9/L, hemoglobin < 8 g/dL, or platelet count < 100 x 10^9/L.

14. Subjects with evidence of active or history of clinically significant endocrine, pulmonary, cardiovascular (including uncontrolled hyperlipidemia [defined as LDL > 200 mg/dL, total cholesterol > 300 mg/dL, triglyceride > 500 mg/dL]), hepatic, GI, psychiatric, oncologic or neurological disease as determined by the investigator at screening.
15. Subjects with an active solid organ or hematological malignancy (except non-melanoma skin cancers), or a history of a solid organ or hematological malignancy within the last 5 years.
16. Subjects with an organ transplant.
17. Subjects who received a live vaccine within 4 weeks of screening visit.
18. Subjects with condition(s) that in the opinion of the study investigators, may interfere with the participants ability to comply with the study procedures.

Concomitant medications

Study subjects will be allowed to remain on permitted concomitant medications provided the patient is on a stable dose for ≥2 weeks prior to starting tofactinib. Patient will need to stay on stable doses of these medications for the study duration of 8 weeks.

1. Antibiotics
2. Antidiarrheal agents
3. Oral corticosteroids including budesonide, up to doses of prednisone 20mg daily (or equivalent), or budesonide 9mg daily.
4. Probiotics

The following medications will not be allowed during the study:

1. Azathioprine, 6-mercaptopurine, or methotrexate within the 28 days prior to dosing visit.
2. Adalimumab, infliximab, golimumab, etanercept, certolizumab or vedolizumab within the 60 days prior to the first study visit or with negative drug concentration
3. Ustekinumab within 120 days prior to the first dosing visit or with negative drug concentration.
4. Intravenous corticosteroids within the 14 days prior to the first dosing visit.
5. Topical mesalamine or topical steroid within the 14 days prior to the first dosing visit.
6. Mycophenolic acid, tacrolimus, or cyclosporine within 60 days prior to the first dosing visit.

Treatment with Tofacitinib

Eligible subjects will be given tofacitinib 10mg twice daily for an 8-week duration. Study drug will be supplied for 4 weeks each at the baseline and week 4 visits.

Study Visits and Procedures

There are 5 study visits and 2 pouch endoscopic procedures during this 12-week study.

Screening Period (Week -4 to Day 0)

After giving informed consent, subjects will undergo up to a 4-week screening period to provide baseline data and be assessed for eligibility. The subjects will have a screening visit during which they will undergo an assessment of their medical history, symptom assessment and a complete physical examination with vital signs, height and weight measurement. They will also undergo complete blood count with automated differential, serum chemistries, serum C-reactive protein (CRP), lipid panel, QuantiFERON®-TB Gold test, urinalysis, fecal calprotectin, infectious stool studies, electrocardiogram (ECG), and chest X-ray. Subjects who satisfy the inclusion criteria and do not meet any exclusion criteria will proceed with pouch endoscopy with biopsies to confirm endoscopic eligibility and assess a baseline mPDAI endoscopic sub-score. The pouch endoscopy will be scored by a central reader to reduce the risk of bias. If the subject meets all the eligibility criteria, he/she may be enrolled into the study. The subjects will be required to maintain a daily paper-based symptom diary starting immediately after the screening visit, although only symptoms during the 3 days preceding the study visits will be used for the calculation of the mPDAI score for the appropriate study visits.

Baseline Visit (Week 0)

At the baseline visit, subjects' eligibility for the study will be confirmed. Vital signs will be recorded, and a targeted physical examination will be performed. The symptom diary will be reviewed for calculation of the mPDAI score, and subjects will complete the CGQL questionnaire. At the end of the visit, the subjects will be given a 4-week supply of tofacitinib to be taken at a dose of 10 mg twice daily.

Week 4 and Week 8 Visit (±3 days)

At the week 4 and week 8 visit, the subjects will undergo assessment for concomitant medication use, adverse effects and compliance with the study drug. Physical assessment will include vital signs and a symptom driven targeted physical examination. Blood, urine and stool will be collected for hematology, chemistry, CRP, urinalysis and fecal calprotectin measurement. Symptom diary will be reviewed, and subjects will complete the CGQL questionnaire. At the end of week 4 visit, the second 4-week supply of the study drug will be dispensed to the subjects. At the end of 8 weeks, the subjects will stop taking the study drug and undergo a pouch endoscopy with biopsies for calculation of mPDAI score to assess treatment response. The pouch endoscopy will be scored by a central reader to reduce the risk of bias.

Week 12 (±3 days) or Early Termination Visit

The week 12 visit will be the final visit. Subjects who are withdrawn earlier from the study (per study rules and subjects who withdraw consent) after receiving study medication will complete

an early termination visit. At this visit, subjects will undergo a physical assessment, review of medications, adverse event assessment and blood, urine and stool collection for hematology, chemistry, CRP, urinalysis and fecal calprotectin measurement. Symptom assessment and CGQL questionnaire completion will also be performed.

Table 1 - Schedule of Study Procedures and Visits

Study visit	Screening (Week -4 to day 0)	Baseline (Day 1)	Week 4	Week 8	Week 12
General					
Informed consent	x				
Medication/Medical History	x				
Smoking Status	x				
Height, weight, BMI	x	x	x	x	x
Vital Signs	x	x	x	x	x
12-lead ECG	x				
Physical Examination	x	x	x	x	x
Chest X-ray	x				
Tuberculosis and HBV testing	x				
Study Drug Dispensing		x	x		
Clinical, laboratory, endoscopic and safety assessments					
Pregnancy Test (females only)	x				
Urine pregnancy test		X	X		
Chemistry, Hematology, Urinalysis	x		x	x	x
Stool C. difficile test	x				
Fasting Lipid Panel	x		x	x	x
C-Reactive Protein	x		x	x	x
Pouch endoscopy and biopsies	x			x	
Fecal calprotectin	x		x	x	x
Symptom Assessments	x	x	x	x	x
Concomitant medications	x	x	x	x	x
mPDAI		x		x	
Adverse event assessment			x	x	x
CGQL		x	x	x	x

Evaluation and Outcomes

The primary outcome of the study is clinical response at 8 weeks (defined below) as a measure of treatment efficacy. Other efficacy endpoints will include individual clinical, biochemical, and endoscopic assessments. Key secondary outcomes include assessment for safety and health-related quality of life.

Primary Endpoint

1. Proportion of subjects with clinical response defined as reduction in mPDAI score ≥2 from baseline at 8 weeks.

Secondary Endpoints

1. The proportion of subjects with clinical response, defined as an mPDAI score of ≥5 at 8 weeks with ≥2-point decrease from the baseline score at 8 weeks.
2. The proportion of subjects with clinical remission at 8 weeks, defined as mPDAI score of <5 with a ≥2-point decrease from the baseline mPDAI score.
3. Change in mPDAI score at 8 weeks compared to baseline.
4. Change in mPDAI clinical sub-score at week 4 and week 8 compared to baseline.
5. Change in mPDAI endoscopic sub-score at week 8 compared to baseline.
6. Change in IBD-related quality of life as measured by Cleveland Global Quality of Life (CGQL) at week 4 and week 8 compared to baseline.
7. Safety, as determined by incidence of treatment-emergent adverse events. Adverse events of interest will include thromboembolic events and herpes zoster.

Efficacy Assessments

Efficacy measurement

The following will be used for definitions of clinical, biochemical, and endoscopic efficacy:

1. Clinical response defined as an mPDAI score of ≥5 at 8 weeks with a 2-point decrease from the baseline mPDAI score.
2. Clinical remission defined as mPDAI score <5 after 8 weeks of treatment.
3. Change in mPDAI score from baseline to week 8.
4. Change in clinical and endoscopic mPDAI sub-scores from baseline to week 8.
5. Change in fecal calprotectin from baseline to week 8.
6. Change in serum C-reactive protein from baseline to week 8.

Symptom Diary

The subjects will be required to maintain a paper-based symptom diary to be completed daily starting after the initial screening visit. The symptoms recorded will include frequency of bowel movements, fecal urgency, abdominal pain/cramps, fever and blood in stools. The symptoms during the 3 days preceding the study visits will be used for the calculation of the mPDAI score for each study visits.

Pouch disease activity

Pouch disease activity assessment will be done using mPDAI, which is a combination of 6-point clinical and 6-point endoscopic scores. It has been shown to have excellent accuracy for pouchitis disease activity assessment with an area under the receiver operative characteristic curve of 0.995 and a sensitivity and specificity of 97% and 100%, respectively, compared to the pouch disease activity (PDAI) score, which is more complex as it includes histological activity

score in addition to clinical and endoscopic scores[17]. mPDAI score will be calculated at each study visit.

Health-related quality of life

Health related quality of life will be measured using the validated CGQL. The CGQL is a 3-question patient-reported assessment, which asks to rate the following questions on a 0-10 scale, with 0 being worst and 10 being best:

1. Current Quality of Life?
2. Current Quality of Health?
3. Current Energy Level?

Patients will be asked to complete the CGQL questionnaire at each study visit.

Laboratory markers

Serum CRP and fecal calprotectin will be used as laboratory markers of pouchitis activity. These will be assessed during the screening period and at week 4, 8 and 12 visits.

Safety Assessment

Subject safety will be assessed on all study visits using standard measures, including vital signs, symptom history, concomitant medication usage history, physical examinations, and blood and urine laboratory tests. Specifically, subjects will be assessed for the known potential adverse events to tofacitinib including anemia, peripheral cytopenias, lipid panel derangements, elevation of liver aminotransferases, thromboembolic events and infections.

Statistical Methods

Sample Size Estimation

Since this is a pilot study, no sample statistical sample size estimation was performed.

Data Analysis

Study subject demographics (age, gender, race), baseline characteristics (height, weight, and BMI), IBD history, prior IBD-related medication use, concomitant medications and baseline laboratory tests will be reported using descriptive statistics. All subjects in the study who received at least one dose of the study drug will be included for analysis. Missing data or early termination will be handled by non-responder imputation. Remission and response rate will be assessed using descriptive statistics. Change in mPDAI, CGQL scores, serum CRP and fecal calprotectin compared to baseline will be assessed using Wilcoxon signed-rank test. Adverse events will also be reported using descriptive statistics. Data will be considered significant at the two-sided p vale of <0.05 where applicable.

Publication Plan

After the completion of the study and analysis of the data, we will submit the results of this study to national gastroenterology meetings (ie. Digestive Disease Week or American College of Gastroenterology Annual Meeting) followed by manuscript submission for publication in a high impact peer-reviewed journal.

Anticipated Project Timeline

Based on the clinical volume at Cedars-Sinai Medical Center, we anticipate enrolling 12 subjects in this research study over a period of 28 months. Last patient study visit will be 12 weeks later. This will be followed by data analysis and writeup/submission of study abstract and manuscript.

Task	Month											
	1-2	**3-4**	**5-6**	**7- 10**	**11 - 14**	**15 - 18**	**19 - 22**	**23 – 26**	**27 - 30**	**31 - 34**	**35 - 36**	**37 - 39**
Obtain IRB approval	○	○										
Enrollment			○	○	○	○	○	○	○	○		
Final study visit				○	○	○	○	○	○	○	○	
Data analysis											○	
Prepare / submit abstract											○	○
Prepare / submit manuscript												○

References

1. Peyrin-Biroulet L, Germain A, Patel AS, Lindsay JO. Systematic review: outcomes and post-operative complications following colectomy for ulcerative colitis. *Aliment Pharmacol Ther.* 2016;44(8):807-816.
2. Lightner AL, Mathis KL, Dozois EJ, et al. Results at Up to 30 Years After Ileal Pouch-Anal Anastomosis for Chronic Ulcerative Colitis. *Inflamm Bowel Dis.* 2017;23(5):781-790.
3. Fazio VW, Kiran RP, Remzi FH, et al. Ileal pouch anal anastomosis: analysis of outcome and quality of life in 3707 patients. *Ann Surg.* 2013;257(4):679-685.
4. Madiba TE, Bartolo DC. Pouchitis following restorative proctocolectomy for ulcerative colitis: incidence and therapeutic outcome. *J R Coll Surg Edinb.* 2001;46(6):334-337.
5. Koerdt S, Jehle EC, Kreis ME, Kasparek MS. Quality of life after proctocolectomy and ileal pouch-anal anastomosis in patients with ulcerative colitis. *Int J Colorectal Dis.* 2014;29(5):545-554.
6. Körsgen S, Keighley MR. Causes of failure and life expectancy of the ileoanal pouch. *Int J Colorectal Dis.* 1997;12(1):4-8.
7. Segal JP, Poo SX, McLaughlin SD, Faiz OD, Clark SK, Hart AL. Long-term follow-up of the use of maintenance antibiotic therapy for chronic antibiotic-dependent pouchitis. *Frontline Gastroenterol.* 2018;9(2):154-158.
8. McLaughlin SD, Clark SK, Tekkis PP, Ciclitira PJ, Nicholls RJ. An open study of maintenance antibiotic therapy for chronic antibiotic-dependent pouchitis: efficacy, complications and outcome. *Colorectal Dis.* 2011;13(4):438-444.
9. Gionchetti P, Rizzello F, Poggioli G, et al. Oral budesonide in the treatment of chronic refractory pouchitis. *Aliment Pharmacol Ther.* 2007;25(10):1231-1236.
10. Navaneethan U, Venkatesh PG, Bennett AE, et al. Impact of budesonide on liver function tests and gut inflammation in patients with primary sclerosing cholangitis and ileal pouch anal anastomosis. *J Crohns Colitis.* 2012;6(5):536-542.
11. Huguet M, Pereira B, Goutte M, et al. Systematic Review With Meta-Analysis: Anti-TNF Therapy in Refractory Pouchitis and Crohn's Disease-Like Complications of the Pouch After Ileal Pouch-Anal Anastomosis Following Colectomy for Ulcerative Colitis. *Inflamm Bowel Dis.* 2018;24(2):261-268.
12. Gregory M, Weaver KN, Hoversten P, et al. Efficacy of Vedolizumab for Refractory Pouchitis of the Ileo-anal Pouch: Results From a Multicenter US Cohort. *Inflamm Bowel Dis.* 2019;25(9):1569-1576.
13. Weaver KN, Gregory M, Syal G, et al. Ustekinumab Is Effective for the Treatment of Crohn's Disease of the Pouch in a Multicenter Cohort. *Inflamm Bowel Dis.* 2019;25(4):767-774.
14. Olivera P, Danese S, Peyrin-Biroulet L. JAK inhibition in inflammatory bowel disease. *Expert Rev Clin Immunol.* 2017;13(7):693-703.
15. Sandborn WJ, Su C, Sands BE, et al. Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis. *N Engl J Med.* 2017;376(18):1723-1736.
16. Kühbacher T, Gionchetti P, Hampe J, et al. Activation of signal-transducer and activator of transcription 1 (STAT1) in pouchitis. *Clin Exp Immunol.* 2001;123(3):395-401.

17. Shen B, Achkar JP, Connor JT, et al. Modified pouchitis disease activity index: a simplified approach to the diagnosis of pouchitis. *Dis Colon Rectum.* 2003;46(6):748-753.
18. Athayde J, Davies SC, Parker CE, et al. Placebo Rates in Randomized Controlled Trials of Pouchitis Therapy. *Dig Dis Sci.* 2018;63(10):2519-2528.