Surgical Management of Ulcerative Colitis in the Era of Biologics: Trends and Risk Factors

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ABSTRACT

Ulcerative colitis is a chronic disease characterized by inflammation of the colorectal mucosa. Surgery for ulcerative colitis is curative, as the disease is limited to the colon and rectum. However, due to its associated morbidity and mortality and with the emergence of new medical therapies, surgical management has shifted from having a central role in the treatment algorithm to an option of last resort. Biologics have revolutionized the care of patients with ulcerative colitis. However, since their introduction as a rescue therapy, there has been debate on their ability to reduce the risk of colectomy for patients with ulcerative colitis. Moreover, because of their immunosuppressive effects, there have been concerns in the literature about their safety post-operatively. Given the equipoise regarding the effect of biologics on the surgical management of ulcerative colitis, we sought to investigate the impact of their introduction on rates of colectomy among patients with ulcerative colitis from Québec, Canada and to identify risk factors for colectomy. We also aimed to describe associated changes in morbidity and mortality post-colectomy.

Two cohorts were defined: the pre-biologics era (1998-2004) and the biologics era (2005-2011). The former was characterized by minimal use of biologics for ulcerative colitis whereas the latter was characterized by increased use of biologics. We found a higher incidence rate of colectomies in the pre-biologics compared to the biologics era. We identified the following risk factors for colectomy: gastro-intestinal hospitalizations in the year prior to diagnosis, male sex, anemia, a history of congestive heart failure and being in the pre-biologics era. We also found that post-operative mortality at 90-days was significantly higher in the pre-biologics compared to the biologics era. Results from this thesis elucidated current trends in surgery for ulcerative colitis in

the era of biologics with regards to incidence rates and predictors. Future research should strive to better identify predictors of failure of medical management and trends in indications for surgery.

RESUMÉ FRANÇAIS

La colite ulcéreuse est une maladie chronique caractérisée par une inflammation de la muqueuse colorectale. La chirurgie pour le traitement de la colite ulcéreuse est curative, puisque cette dernière est limitée au côlon et au rectum. Cependant, en raison de la morbidité et la mortalité associées à cette intervention, et surtout avec l'émergence de nouvelles thérapies médicales, la chirurgie a passé d'un rôle central dans l'algorithme de traitement à une option de dernier recours. Les agents biologiques sont à l'avant-garde des traitements qui ont révolutionné la prise en charge de ces patients. Par ailleurs, depuis leur introduction pour usage comme thérapie de sauvetage pour les patients atteints de colite ulcéreuse, il existe un débat concernant leur capacité à réduire le risque de colectomie. De plus, en raison de leurs effets immunosuppresseurs, des préoccupations existent concernant leur usage en période péri-opératoire. Compte tenu de l'incapacité des études à conclure sur leur effet, nous avons cherché à étudier l'impact de l'introduction des agents biologiques sur le marché sur les taux de colectomies chez les patients atteints de colite ulcéreuse au Québec, Canada et d'identifier les facteurs qui prédiraient le risque d'une intervention chirurgicale. Nous avons également cherché à décrire les changements associés à la morbidité et la mortalité post-colectomie après l'introduction de ces agents biologiques afin de mieux évaluer leur effet en période post-opératoire.

Deux cohortes ont été définies: l'ère pré-biologique (1998-2004) et l'ère biologique (2005-2011). L'ère pré-biologique est caractérisée par une utilisation minime d'agents biologiques pour la colite ulcéreuse alors que l'ère biologique est caractérisée par une utilisation élevée d'agents biologiques. Nous avons trouvé un taux d'incidence de colectomies plus élevé dans l'ère pré-biologique par rapport à l'ère biologique. Nous avons identifié les facteurs de risque pour la

colectomie qui comprenait les hospitalisations pour raisons gastro-intestinales durant l'année précédant le diagnostique, le sexe masculin, l'anémie, un antécédent d'insuffisance cardiaque congestive et l'ère pré-biologique. Nous avons également constaté que la mortalité post-opératoire à 90 jours était significativement plus élevée durant l'ère pré-biologique comparée à l'ère biologique. Les résultats de cette thèse ont élucidé le risque de chirurgie pour la colite ulcéreuse après l'introduction des produits biologiques en ce qui concerne l'ampleur et prédicteurs. Des avenues de recherche futures devraient viser à mieux identifier des facteurs qui prédiraient l'échec médical ainsi que d'identifier les changements d'indications chirurgicales de la colectomie.

FORMAT OF THE THESIS

This is a manuscript-based thesis written in compliance with the guidelines and specifications detailed by the Faculty of Graduate and Postdoctoral studies of McGill University. The thesis begins with an introductory chapter (Chapter 1) containing relevant background information and a review of the published literature. Chapter 2 is based on a manuscript by Abou Khalil M, Boutros M and Rahme E and is pending medical journal submission. Chapter 3 contains supplementary analyses and Chapter 4 summarizes findings and contains a general discussion of the results and how they relate to future research avenues.

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PREFACE & CONTRIBUTION OF AUTHORS

Maria Abou Khalil (Thesis candidate):

I was responsible for generating variables of interest and comparing them to the variables created by Mr. Hacene Najjar. I was also responsible for the data analysis, literature review and writing of this thesis document.

Elham Rahme (Supervisor):

Dr. Rahme regularly provided insight into the study design, methodology and interpretation of the statistical analyses. Dr. Rahme reviewed the thesis document and manuscript.

Marylise Boutros (Co-Supervisor):

Dr. Boutros provided insight into clinically relevant topics in colorectal surgery, and insight into study design, methodology and interpretation of data. Dr. Boutros reviewed the thesis document and edited the manuscript.

Hacene Najjar (Bio-Statistician):

Mr. Najjar provided help in constructing the two cohorts, applying inclusion and exclusion criteria and generating key variables.

CHAPTER 1: INTRODUCTION

Defining Ulcerative Colitis

Ulcerative colitis (UC) is an inflammatory bowel disease (IBD) characterized by chronic inflammation of the colon and rectum that is limited to the mucosa. Unlike UC, Crohn's disease (CD), the other entity within IBD, is characterized by transmural inflammation that can occur anywhere in the gastro-intestinal (GI) tract. These distinguishing characteristics allow surgery to be used with curative intent for UC, while only for management of complications for CD.

The inflammation in UC always involves the rectum (ulcerative proctitis) and can extend proximally and circumferentially to involve the left colon (left sided UC), or extend proximal to the splenic flexure (pancolonic UC) (1). Proximal extent of disease in UC is not constant and can change over time. In fact, it is estimated that proximal extension of ulcerative proctitis can occur in 50% of patients over 10 years, and is reported to be even higher in left sided UC (2). True to the dynamic nature of the disease, the degree of inflammation can decrease or increase over time. Pathognomonic endoscopic findings in UC are related to mucosal inflammation and include erythema and loss of mucosal vascular markings, ulcers, granular and friable mucosa and pseudopolyps (3).

The incidence of UC varies with geographic location. It is estimated that the annual incidence of UC is the highest in Westernized countries, with rates reported from Canada at 19.2 cases per 100,000 person years from a study of five provincial health databases published in 2006 (including the provinces of British Columbia, Alberta, Saskatchewan, Manitoba and Nova Scotia) (4, 5). Results from a provincial administrative database in Québec published almost a decade later reported a lower incidence rate of UC in Québec at 10.1 cases per 100,000 person-years (6). The difference in incidence rates may be due, at least in part, to different case definitions of UC used in these two studies. Results of a systematic review published in 2012 found a statistically significant increase in the incidence of UC across the majority of studies, with only 6% of studies reporting a significant decrease in the incidence rate (5). This apparent increase may be due to environmental factors or improvements in diagnostic methods and underlines the importance of continuing research in this field (5).

Given the chronicity UC and its burden on the individual and the healthcare system with significant health service utilization and associated cost, it remains important to understand its evolution (7-10).

Clinical presentation, diagnosis and scoring systems

Patients with UC typically present with rectal bleeding, loose stools and colicky abdominal pain. Associated symptoms also include tenesmus, urgency and mucous mixed with stools (2).

The non-specific GI symptoms that patients can present with can be a challenge in differentiating UC from other GI disorders. Although clinical history and serological markers can help in diagnosis, the gold standard for the diagnosis of UC remains colonoscopy with biopsy and histological confirmation (11). Patients with UC can have a wide scope of disease activity ranging from mild to severe disease. Different disease severity classifications exist, and all categorize UC from asymptomatic to severe disease based on factors such as number of bowel movements, systemic signs of disease and serologic markers (1, 12). According to the Montreal Classification of IBD, mild UC is characterized by the absence of systemic illness with normal serologic inflammatory markers and up to 4 bowel movements a day (1). This is compared to moderate UC, which is characterized by having more than 4 bowel movements a day with signs of systemic toxicity. Severe UC is defined as having six or more bloody bowel movements per day, a heart rate of 90 beats/min or above, a temperature of at least 37.5°C, a hemoglobin of less than 10.5g/100mL and an erythrocyte sedimentation rate of at least 30mm/h (1).

Pathophysiology

Although the pathophysiology of UC remains incompletely elucidated, it is thought to arise from an unregulated immune response within the large bowel in a genetically susceptible host (13). Pro-inflammatory cytokines such as interleukins (IL-4, 5, 6,10) and tumor necrosis factor alpha (TNFα) were found to be at the core of the pro-inflammatory uncontrolled autoimmune response (13-15). Understanding the importance that TNFα plays in this inflammatory process has allowed for the development of targeted antibody therapies against this cytokine. These therapies

are part of the class of medications called biologics, characterized by complex structures and derived from microorganisms.

Medical management

Different classes of medications can be used to treat UC, and are often added in a stepwise manner with increasing disease complexity. They include corticosteroids, aminosalicylates, immunomodulators and biologics. Stages of medical management may be categorized as: induction, maintenance and remission. Success of long-term medical management is determined by clinical and endoscopic remission in the absence of steroids (16). Practice guidelines indicate that the first line treatment for patients with mild to moderate disease consists of 5-aminosalicylate (5-ASA) as an oral or rectal formulation (16). Corticosteroid therapy is reserved for patients with mild to moderate disease who fail 5-ASA or to induce patients with moderate to severe UC (16). Long-term use of corticosteroids is not recommended due to their potential deterimental side effects. Thus, after patients achieve clinical response on corticosteroids, they should be transitioned to maintenance agents (5-ASA, immunomodulators and/or biologics) (16).

Biologics have revolutionized the care of patients with UC (17). Infliximab, a monoclonal antibody targeting TNFα was extensively studied and approved for CD prior to demonstration of its efficacy in UC (18, 19). Although there are many biologics available for UC, infliximab is the most studied; its promising results have initiated investigative research into other agents. Although early small randomized controlled trials (RCTs) failed to demonstrate the

efficacy of infliximab (likely due to small sample size or early termination due to poor accrual), larger RCTs have later shown its benefit in this patient population (20-25). Two large multicenter RCTs (Active Colitis Trials, ACT-1 and ACT-2) that demonstrated success of infliximab in treating moderate to severe UC patients were the main drivers behind the Federal Drug Administration (FDA) in the United States and Health Canada's approval in 2005 for its use in patients who have failed conventional treatments (26-28). Although not approved for coverage by the provincial drug insurance plan for patients with UC in the province of Québec, Canada, infliximab and other similar biologics may reimbursed for UC in patients who have failed other treatment regimens; in such situations, physicians are required to fill an "exceptional patients" form to receive approval for prescription reimbursement (29, 30).

Surgical management

Despite advances in medical management, surgery remains an important part of the care of patients with UC (31). Indications for surgery include failure of adequate medical management, adverse effects of medical therapy, development of complications or patient preference. Failure of medical management may include steroid-refractory disease, unresponsiveness to biologics or delayed tolerance to these agents (17). Complications necessitating surgery may include fulminant severe colitis or the development of colorectal dysplasia/neoplasia, the risk of which is higher in patients with UC compared to the general population (32, 33).

Since UC is limited to the colorectal mucosa, performing a total proctocolectomy (removal of the colon and rectum) is considered curative. When surgery for UC is indicated, the type of surgery and reconstruction performed vary depending on the clinical state of the patient and surgeon expertise and preference. In its essence, the surgical management involves removal of the colon and rectum, with the possibility of a reconstruction to create a neo-rectum using small bowel (ileal pouch) which is then anastomosed to the anus, creating an ileal pouch-anal anastomosis (IPAA). Reconstruction can be performed in one, two or three stages. A one-stage operation involves a total proctocolectomy (TPC) with an IPAA reconstruction in the same operation. A two-stage procedure consists of a TPC and IPAA with the addition of a diverting loop ileostomy. This loop ileostomy is reversed in the second part of the two-stage procedure at a later date. The loop ileostomy diverts fecal stream and can protect the anastomosis. A three-stage procedure consists of a total abdominal colectomy (TAC), which is followed in the second stage of the procedure by a completion proctectomy with IPAA and diverting loop ileostomy. The diverting loop ileostomy is reversed in a third surgery. In the elective setting, a two-stage procedure is the standard of care as long as the patient has no signs of malnutrition, significant anemia or recent high dose steroid exposure. In select individuals and situations, some surgeons may offer a one-stage procedure. In the emergent setting, and for patients who have received high dose steroids or immunosuppressive agents, a three-stage procedure is usually preferred. This is especially true for patients who are malnourished or in whom CD has not been excluded (34).

Complications after IPAA are not uncommon and it is reported that 5 to 10% of IPAA procedures fail (35). Post-operative complications can be significant and may impact pouch function. The risk of pouch related pelvic sepsis was reported to be 15.6% at one year and septic

complications were associated with a pouch failure rate of 29% (36). IPAA was also associated to decreased fecundity and pregnancy rates in several studies, although recent studies have shown improved fertility rates with the use of in-vitro fertilization (37-39). Furthermore, even after successful pouch reconstruction, patients are liable to long-term complications. The most common long-term complication is pouchitis, characterized by a relapsing inflammation of the pouch mucosa, which can arise in up to 40% of patients (35). For most patients, this may occur once or a few times over their lifetime, while a minority of patients have chronic pouchitis. Another reason for long-term pouch failure is the development of earlier unrecognized CD. For the aforementioned reasons, though surgery for UC is curative, for many patients it is reserved as a last resort.

Rates of surgery

Several studies have reported decreased rates of surgery in the past decades, however this decrease was not consistent throughout all studies and geographic areas (Tables 1.1 and 1.2) (40-53). Results from a population based multi-institutional Swedish study with patients diagnosed between 1955 to 1984 reported 5, 10 and 25-year cumulative colectomy rates to be 20%, 28%, and 45% respectively (54). In 2008, Solberg *et al*. published results from a Danish population based study that followed patients with newly diagnosed UC, accrued between 1990 and 1993 for up to 10 years, and reported colectomy rates at 1, 5 and 10 years to be 3.5%, 7.5% and 9.8%, respectively (43). When comparing these two large Scandinavian studies published almost decades apart, it appears that even long before the use of biologics for UC, colectomy rates had been decreasing. In more recent years, several population-based

cohort studies have demonstrated overall decreased rates of colectomy without addressing the issue of biologics (44-46). However, due to their ability to induce and maintain remission, biologics may impact colectomy rates, thus making these drugs an interesting subject of study on a population-level.

Supporting the evidence for the efficacy of infliximab, follow-up results at 54 weeks from the ACT-1 and ACT-2 trials showed a significant decrease in colectomy rates in patients treated with high dose infliximab (10mg/kg) compared to placebo, with a cumulative incidence of 10% for infliximab and 17% for placebo (p=0.020) (55). These results were corroborated by other retrospective and prospective studies with short follow-up periods (56, 57).Of note, ACT-1 included patients who failed 6-mercaptopurine and prednisone while ACT-2 included those who failed aminosalicylates, this resulted in a different disease severity mix for the combined results. Patients from the ACT-2 trial drove the decreased rates of colectomy indicating that the decrease in risk of colectomy due to biologics depends on disease severity. However, to date, trials with longer follow up times were unable to demonstrate a sustained significant decreased risk of colectomy with biologics (58-60).

Mortality rates

It is no surprise that the past decades have seen improvements in mortality for patients with UC brought forth by medical advancements. However, it remains unclear how biologics have impacted the rates of mortality. Decreasing mortality rates from acute severe colitis have been documented: from over 70% at one year in 1933 to 20-25% at one year in the 1950s when the importance of timely urgent colectomy was first recognized (61, 62). These mortality rates

continued to decrease with improved medical and surgical care. Furthermore, with the recognition of the importance of hospital expertise and volume, mortality after colectomy for UC continued to improve (63). A study from Scotland used a national linkage database between 1998-2000 and reported 3-year crude mortality rates after emergency colectomy of 9.0% (64). Evaluating immediate post-operative mortality, a US study using the National Inpatient Survey (NIS) from 1995-2005 found a 30-day post-operative mortality rate of 2.3% for colectomies with unknown acuity (63). In view of the increasing use of biologics and concerns regarding their peri-operative safety, it is important to describe trends in post-operative death before and after the introduction of these agents (65).

Aims

Thus, the aim of this study was to investigate the impact of the introduction of biologics on rates of colectomy and post-operative mortality among UC patients from Québec, Canada.

Table 1.1- Studies reporting rates of colectomy for Ulcerative Colitis over time						
Author, Year	**Country**	**Study design**	**Cohort definition**	**Follow up**	**N**	**Colectomy Rates**
Leijonmarck *et al.,*1990	Sweden	Population based cohort	Incident UC diagnosed between 1955-1984	12.7 years (median)	568	5 year: 20% 10 year: 28% 25 year: 45%
Vind *et al.*, 2006	Denmark	Population based cohort	Patients with UC diagnosed between January 2003 and January 2006	1 year	326	1 year: 6%
Hoie *et al.*, 2007	Greece, Israel, Italy, Spain, Denmark, Norway, The Netherlands	Population based cohort	Patients with UC diagnosed between Oct 1, 1991 and Sep 30, 1993	10 years	690	10 year: 8.7%
Solberg *et al.*, 2008	Norway	Population-based cohort study	Incident UC diagnosed between Jan 1, 1990 and Dec 31, 1993	Up to 10 years	519	1 year: 3.5% 5 year: 7.6% 10 years: 9.8%
Williet *et al.*, 2011	France	Population based cohort	Patients with UC diagnosed between years 2000-2008	10 years	151	1 year: 1.3% 5 year: 13.5% 10 year: 38.2% 20 years: 25.4%
Kaplan *et* al., 2012	Canada	Retrospective chart review	Patients with UC who had a colectomy between Jan 1 1997 and Dec 31 2009	-	439	**Reported Annual Percent Change:** -4.3%
Targownik *et al.*, 2012	Canada	Population based cohort study	Patients with UC diagnosed between 1982 and 2008	Up to 20 years	3752	5 year: 7.6% 10 year: 10.4% 20 year: 14.8%
Samuel *et al.*, 2013	USA	Population based cohort	Patients with UC diagnosed between 1970 and 2004	13.9 years (median)	369	1 year: 3.8% 5 years: 13.1% 10 years: 18.9% 20 years: 25.4%
Vester-Andersen *et al.*, 2014	Denmark	Population-based cohort study	Incident UC diagnosed between Jan 1, 2003 and Dec 31, 2004	Minimum 7 years	300	5 years: 10.4% 7 years: 12.5%
Ronnblom *et al.*, 2016	Sweden	Population based cohort study	Patients with UC diagnosed between 2005 and 2009	5 years	524	5 year: 5.3%

Table 1.2- List of studies comparing rates of colectomies for Ulcerative Colitis in different cohorts								
Author	**Country**	**Follow up**	**Study design**	**Cohorts**	**N**	**Colectomy Rates**		
						1-year	**5-year**	**9-year**
Rungoe *et al.*, 2014	Denmark	Up to 32 years	Population based cohort study Patients with UC divided in four cohorts by years of diagnosis	1979-1986	4,845	7.7%	11.7%	14.5%
				1987-1994	5,587	7.0%	11.8%	14.8%
				1995-2002	10,155	4.7%	8.4%	10.4%
				2003-2011	15,195	4.0%	7.5%	9.1%
Jeuring *et al.*, 2015*	The Netherlands	Up to 20 years	Population based cohort study Patients with UC diagnosed at three time periods	1991-1997	476	4.1%	7.5%	
				1998-2005	587	0.9%	5.7%	
				2006-2010	598	1.0%	4.1%	
Author	**Country**	**Follow up**	**Study design**	**Cohorts**	**N**	**Cumulative incidence**		
Moore *et al.*, 2013	Canada	-	Population based cohort study Patients with UC included in the pre-infliximab (2003-2006) or post-infliximab era (2007-2010) by date of entry	2003-2006	5,858	9.97/100 UC patients		
				2007-2010	7,828	8.88 /100 UC patients		
Author	**Country**	**Follow up**	**Study design**	**Cohorts**	**N**	**Annual percent change**		
Reich *et al.*, 2014	Canada	-	Retrospective chart review Patients with UC who underwent a colectomy in two time periods	1998-2005	296	4.4%		
				2005-2011	185	-16.1%		

CHAPTER 2: INCIDENCE RATES AND PREDICTORS OF COLECTOMY FOR ULCERATIVE COLITIS IN THE ERA OF BIOLOGICS: RESULTS FROM A PROVINCIAL DATABASE

M. Abou Khalil, M. Boutros, E. Rahme

Introduction

During the past two decades, significant improvements in the medical management of UC have occurred. Randomized controlled trials (RCTs) such as the Active Ulcerative Control Trials 1 and 2 (ACT 1 and 2) have demonstrated a significant benefit of infliximab, an anti-TNFα biologic agent, for the induction and maintenance of remission for UC (26). Extension studies for these trials have shown that compared to placebo, infliximab therapy decreased the hazard of colectomy at 54 weeks of follow-up by 41% (55). Similar results demonstrating a reduction in urgent colectomies on the short term have been reported by other studies (21, 66). Moreover, Gustavsson *et al*. published 3 year follow-up results from the Swedish-Danish controlled infliximab study and concluded that the favourable short-term decrease in colectomy was also maintained at 3 years for patients in the infliximab group compared to placebo (50% vs. 76%, p=0.02) (60). However, the impact of biologics on the rates of colectomy for longer follow-up times and on a population level remain unclear; this being especially relevant given the chronicity of the disease in question.

In recent years, many groups have looked at trends in colectomy rates in patients with UC. Results of the Inflammatory Bowel Disease in Southeastern Norway (IBSEN) study which followed a cohort of patients with UC from 1992 found a cumulative colectomy rate of 9.8% at 10 years (43). This rate was lower than an earlier report by Langholz *et al.* who observed a colectomy rate of 25% at 10 years following UC diagnosis (67). In Canada, a provincial database study conducted in Manitoba between 1982 and 2008, observed a 5-year and 10-year risk of colectomy at 7.5% and 10.4% respectively (46). In order to understand whether the observed trends in reduced colectomy rates were due to the introduction of biologics, many ecologic studies have reported the rates of colectomy with increased utilization of biologics, but results were conflicting (51-53).

The aim of our study was to assess the impact of biologics on colectomy rates among UC patients in Québec, Canada using a provincial administrative database. Our primary objective was to evaluate the long-term incidence rates of colectomy in the pre-biologics and biologics eras, and to identify risk factors for colectomy. Our secondary objective was to study the post-operative risk of mortality in both eras. Other outcomes of interest were post-operative intensive care unit (ICU) stay and length of hospital stay. We hypothesized that the incidence rates of colectomy have decreased after the introduction of biologics, but given the complexity of patients who underwent surgery in the biologics era, we hypothesized that these patients would have higher mortality rates compared to those who had a colectomy in the pre-biologics era.

Methods:

Data source:

Canadians benefit from a universal health care system that offers coverage for both inpatient and outpatient medical services. In the province of Québec, health service utilisation data is managed by the provincial health insurance agency, the Régie d'Assurance Maladie du Québec (RAMQ). Québec residents must be covered by a drug insurance plan, either provided by private agencies or RAMQ. Private plans are acquired through an individual (or spouse or parents)'s employment. If Québec residents do not have private drug insurance, are 65 years of age or older, or benefit from social assistance they are eligible for the Public Prescription Drug Insurance plan provided by the RAMQ (68). Data was obtained from the RAMQ database from January 1, 1997 to March 31, 2012 for individuals who had at least one UC diagnosis (international classification of disease, ICD-9th revision code 556.x or ICD-10th revision code K51.x) or Crohn's disease (CD) diagnosis (ICD-9th revision code 555.x or ICD-10th revision code K50.x) and had at least one day of drug coverage from RAMQ during that time period. Data included information on demographics, medication prescriptions, physician claims and hospital records (69). Linkage to the physician claims database and the hospital discharge abstract database was possible through a unique patient identifier. Provincial Ethics approval by the Commission d'accès à l'information was obtained for permission to use and link these databases, and this study was approved by the McGill University Health Center Ethics Review Board.

Cohort definition:

Case definition of UC was based on a validated population-based definition developed using the provincial database in Alberta, Canada (70). Accordingly, an individual was labelled as having UC if they had one hospitalization where UC was the primary or secondary discharge diagnosis or 4 physician billings for UC within a 2-year period. Patients who had received both a diagnosis of UC and CD in a two year period were classified as having one or the other based on a validated cumulative scoring system (70). The pre-biologics and biologics eras were defined as January 1, 1998 - December 31, 2004 and January 1, 2005- December 31, 2011, respectively. A cut-off date of January 1, 2005 was used to define these eras since the Federal Drug Administration (FDA) in the United States and Health Canada approved infliximab, the most studied and commonly used biologic agent, for UC patients in 2005 (53). Use of biologics was very low in Québec before 2005. Of all patients covered with the public drug insurance plan, only 21 patients with UC in the pre-biologics era compared to 931 patients with UC in the biologics era used anti-TNFα medications. Two retrospective UC cohorts were constructed in the pre-biologics and biologics eras, respectively. Patients in these cohorts were followed from index date until colectomy, death or the end of the study period. The patients' index date was defined as the first available diagnosis date of UC within the study period.

Exclusion Criteria:

Patients who had a prior colectomy or any abdominal surgery which may indicate that they had a remote colectomy (such as de novo creation of a pouch or reversal of loop ileostomy) or

any diagnosis of UC or CD in the year prior to their index date were excluded to allow for a one-year washout period.

Definitions:

Outcome: The primary outcome colectomy was a hospitalization for colectomy defined as a hospitalization during which a physician claim for a colectomy was filed (RAMQ procedure codes provided in Appendix 1). These included claims for total colectomy, total proctocolectomy with end ileostomy or with ileal pouch anal anastomosis (IPAA). Claims for segmental colectomies were not included. The date of the physician claim for colectomy was considered the colectomy date. Post-operative death was defined as death within 90 days of the colectomy.

Patient characteristics: considered patient characteristics included age, sex and comorbidity (including hypertension, diabetes, ischemic heart disease, congestive heart failure, cardiovascular disease, atrial fibrillation, anemia, peptic ulcer disease and cancer). Also available from RAMQ is an index of socioeconomic status and indices of material and social deprivation developed by the Québec national public health institute (INSPQ) and used as markers of socio-economic status (71, 72). The social deprivation index includes information on living and marital status and the material deprivation index includes information on post-secondary education, employment, and average income (71). Both the material and social indices are classified in quintiles from the most favourable (Quintile 1) to the least favourable (Quintile 5). For this study, three levels of material and social deprivation were constructed (Low deprivation (Quintile 1), Medium deprivation (Quintiles 2 and 3), or High deprivation (Quintiles 4 and 5). Patients' postal codes were used to determine rural or urban

residence. This was determined by the second character of the three digit postal code provided by the RAMQ with 0 indicating a rural Postal code and any other number indicating an urban postal code (73). Hospitalizations for gastrointestinal (GI) reasons were those were a primary or secondary diagnosis defined by ICD-9th or ICD 10th revision codes outlined in Appendix 2 occurred. Medical comorbidities were assessed from hospitalization records and physician claims by ICD-9th or ICD-10th revision codes during the year prior to the index date (Appendix 3).

Statistical analyses:

A multivariate logistic regression model using backward selection was fit to compare patient baseline characteristics between the two study periods. Kaplan-Meier curves were constructed to display unadjusted time to colectomy in the two study periods and Survival analyses were performed using Cox proportional hazards (PH) models for each of the outcomes of interest: colectomy and death. Differences between Kaplan Meier curves were tested using the log-rank test. Multiple univariate Cox PH regression analyses were first performed to identify confounders that may impact the outcomes of interest. These were kept in the final multivariate model in a backward selection if the p value was < 0.10. Other outcomes of interest such as post-operative intensive care unit stay and length of hospital stay among those who had a colectomy were compared using Student's t-test and χ^2 tests for continuous and categorical variables, respectively. Statistical significance was defined as $p<0.05$. All statistical analyses were performed using STATA statistical software version 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Results:

The initial search revealed 5,102 UC patients in the pre-biologics era and 5,410 patients in the biologics era. After applying the exclusion criteria, 2,829 were included in the pre-biologics era and 3,313 remained in the biologics era.

Table 2.1 presents patient baseline characteristics. Patients in the pre-biologics era were slightly younger than those in the biologics era (48.82% vs. 50.66%; odds ratio, OR, 95% confidence interval, CI for one-year increase 1.01; 1.00-1.01) and had a slight male predominance (51.64% vs. 48.85%; 0.90, 0.81-1.00). Medical comorbidities that were similar in both eras included a diagnosis of cancer, atrial fibrillation, cardiovascular disease, congestive heart failure and hypertension. The prevalence of ischemic heart disease was decreased in patients in the biologics period (9.92% vs. 11.67; 0.69, 0.57-0.85). On the contrary, prevalence of diabetes in patients in the pre-biologics era was decreased compared to the biologics era (7.39% vs. 10.81%; 1.50, 1.23-1.83). Urban residence, the prevalence of anemia and GI hospitalizations for the year prior to the index episode as well as social and material deprivation indices were similar in both periods.

Colectomy

Of the 2,829 patients in the pre-biologics era, 335 patients underwent a colectomy, compared to 314 patients of the 3,313 patients included in the biologics era. Median time of follow-up (first and third quartiles) was similar in both periods: 3.38 (1.56, 5.21) years for the pre-biologics era, and 3.29 (1.68, 5.14) years in the biologics era (p=0.206). The incidence rate of

colectomies in the pre-biologics era was 36.08/1000 patient years, compared to 29.99/1000 patient years in the biologics era, with an incidence rate ratio of 0.80 (95%CI [0.69-0.94]). As seen in the Kaplan-Meier curves in Figure 2.1, the unadjusted probability of colectomy in both eras was different (log-rank: p=0.004), and steadily increased over the follow-up period. Rates of colectomy at 5-years estimated from Figure 2 revealed a probability of colectomy of 14% in patients in the pre-biologics era compared to 12% in patients in the biologics era.

Results of the univariate and multivariate Cox PH regression model are detailed in Table 2.2. After adjusting for potential confounders, the biologics era was associated with a significantly decreased hazard of colectomy (hazard ratio, HR; 95%CI= 0.81; 0.70-0.95). Other predictors of colectomy included presence of anemia (1.66; 1.38-2.01), GI hospitalizations in the year preceding the index episode (1.24; 1.04-1.47), congestive heart failure (2.08; 1.27-3.40) and male gender (1.47; 1.26-1.72). Factors that decreased the hazard of colectomy were ischemic heart disease (0.62; 0.45-0.87) and diabetes (0.64; 0.46-0.90).

Post-operative death

Of the patients who underwent a colectomy, 27 (8.06%) in the pre-biologics era and 10 (3.18%) in the biologics era died within 90 days of their colectomy. The Kaplan-Meier curve for probability of survival depicts this difference in post-operative death with a higher probability of survival in the biologics era (log-rank: p=0.007). For this secondary outcome of post-operative death, results of the univariate and multivariate Cox PH regression model are detailed in Table 2.3. After adjusting for potential confounders, age at index date, GI hospitalization in the year prior to the index date and having been in the pre-biologics era remained associated with an increased hazard of death. With every year increase in age, there

was an 8% increased hazard of post-operative death. Patients with GI hospitalizations in the previous year had a 441% increased hazard of death within 90 days of colectomy. Patients who were in the biologics era had a 57% decreased hazard of post-operative death compared to patients in the pre-biologics era.

Hospital stay and ICU admissions

Median length (first and third quartiles) of post-operative hospital stay was 12 (8,18) days for patients in the pre-biologics era, and 11 (7,20) days for patients in the biologics era (p=0.66).

The proportion of patients who had a colectomy during an admission that was from the emergency department (ED) was similar in both pre-biologics and biologics eras (51.18% vs. 49.19%, p=0.613).

Out of the 335 patients who had a colectomy in the pre-biologics era, 122 patients (36.42%) were admitted to the ICU at least once during their hospitalization, compared to 96 patients out of the 314 in the biologics era (30.67%). The crude risk ratio of ICU admission was 0.84, signifying that patients in the biologics era had a 13% decreased risk of requiring ICU admission compared to patients in the pre-biologics era, although that result did not reach statistical significance (p=0.109). Median days (first and third quartiles) in the ICU were 4 (2, 10) for patients in the pre-biologics era compared to 3 (2, 8) days for patients in the biologics era (p=0.587).

Discussion

Although the introduction of biologics revolutionized the care of patients with UC, studies have disputed their long-term impact on rates of colectomy. In specific, there remains a concern that excellent short-term remission may result in delayed colectomies and thus translate into unchanged long-term rates of colectomy. Indeed, this was the case 26 years ago with the introduction of cyclosporine for UC. Lichtiger *et al*., initially demonstrated a response of 82% and a significant reduction in short-term colectomy rates with the use of cyclosporine for severe UC (74). However, in 2005, Campbell *et al*. observed that over 7 years, 53% of patients who received cyclosporine ultimately required a colectomy (75). Limited long-term data exists regarding the risk of colectomy on a population level in the biologics era. In this study, we compared the biologics era, characterized as the years during which there was an increased use of biologics in Québec, to the preceding era of similar length where biologics use was minimal. In the pre-biologics cohort, no patient used anti-TNFα in the year preceding his or her index date. We observed a significantly decreased 5-year rate of colectomy in the biologics era compared to the pre-biologics era (14% vs. 12%, log rank $p<0.001$). Similar to these findings, Moore *et al*. published in 2014 their results using a provincial database in British Columbia, Canada (52). The authors compared the incidence proportion of surgery in the three years preceding and following the introduction of infliximab. The incidence proportion of colectomy was decreased in the latter years (8.88% vs. 9.97%, $p= 0.03$); this risk was calculated by dividing the number of colectomies performed during the period of interest by the number of patients with UC during the 3 years. However, these frequencies cannot be directly compared to the incidence rates and cumulative probability of colectomy we reported in this study, which were obtained with consideration of

patient censoring by using a survival analysis. In 2014, Reich *et al*. attempted to assess the impact of biologics on the rates of colectomies (53). Using a multicenter retrospective chart review, they identified patients who underwent colectomies for UC in four hospitals from 1998-2011. The authors expressed colectomy rates by dividing the total annual number of identified colectomies from chart review by an estimate of the number of UC patients at risk using the prevalence of UC from population statistics. Similar to our study, the authors defined pre-biologics and biologics eras by a cut-off at 2005. The authors observed that the change in annual colectomy incidence rates were not significant in the pre-biologics era, whereas there was a significant net decrease in annual incidence of colectomies in the biologics era. However, due to the study design, the authors could not report overall long-term incidence rates of colectomies in both eras. Thus, in order to better capture the incidence rate of colectomies for UC, researchers have turned to population-based data.

Using a Danish population database, Rungoe *et al*. published similar results that spanned 25 years from 1979 to 2011 (50). The authors divided patients into four equal time periods based on year of UC diagnosis. They observed decreased cumulative probabilities of surgery at 1, 5 and 9-years after diagnosis in the later cohorts accompanied by an increase in use of biologics and immunomodulators. Contrary to these findings and to our results, in 2015 Jeuring *et al*. published results from their population based cohort study in the Netherlands (51). Biologics were approved for UC in the Netherlands in 2006, thus patients were divided into 3 cohorts: 1991-1997, 1998-2005 and 2006-2010. The authors divided rates into early (less than or at 60 days from diagnosis) and late colectomies (more than 60 days from diagnosis), however they did not report an overall colectomy rate. For early colectomies, the authors found that there

was a significant decline in rates between the first and second time period, but not thereafter. For late colectomies, the authors observed stable rates throughout the entire study. These findings indicate that although biologics use may have impacted short-term rates, long-term colectomy rates have remained stable, and this could be especially true in patients who have severe disease. To date, even well designed large population-based studies have not agreed regarding the impact of biologics on long-term incidence rates of colectomy. In our study, using population-based cohorts with stringent inclusion and exclusion criteria, defined pre- and biologics eras and long follow-up periods (median of 3 years), we observed a significant decreased rate of colectomy after the introduction of biologics.

In our study, male gender, GI hospitalizations, anemia and congestive heart failure were found to increase the risk of colectomy. Conversely, diabetes, ischemic heart disease and being in the biologics era decreased the risk of colectomy. Our findings of increased risk for colectomy in men was in concordance with previously published studies (46). Although not reported in the literature, it is plausible that this observation is due to women and their physicians' hope to delay surgery for as long as possible due to the reported decline in fertility with surgery for UC (37). Although some studies found young age to be a risk factor for colectomy, these results were not reproduced in our study (43, 76). This may be due to a limitation of our study, in that our study cohort was restricted to patients with at least one day of coverage from the public insurance plan, thus not representative of the proportion of the young working population who are covered by private insurance plans. Patients with anemia were at increased risk of a colectomy in our cohort. This is likely due to anemia being a marker of disease severity. Similarly, prior GI hospitalizations were predictors of colectomy. After adjusting for confounders, the biologics era remained associated with a decreased risk of

colectomy. To our knowledge, this is the first population-based study to report a decreased risk of colectomy in the biologics era.

Biologics play an integral role in inhibiting the inflammatory response essential for healing. Due to these immunosuppressive effects, many studies have attempted to establish if patients on these agents were at increased risk of post-operative complications. For the most part studies have shown conflicting results with some demonstrating increased post-operative complications and others observing no impact on complications (65, 77-79). Given the available data, we chose to assess the 90-day post-operative mortality, length of stay and risk of ICU admissions as markers of post-operative morbidity. Although we hypothesized that patients who underwent a colectomy in the biologics era would be more ill due to the increased medical rescue therapy options compared to the pre-biologics era, our results demonstrated a decrease in overall post-operative mortality at 90 days in the biologics compared to the pre-biologics era after adjusting for potential confounders. Although the Kaplan-Meier curves did not seem to differ in mortality up to 14 days post-operatively, there is a clear survival benefit in the biologics era thereafter. As expected, age remained an independent predictor of mortality at 90-days post-operatively. Post-operative length of hospital stay and ICU admissions were not significantly different in both groups. These outcomes, chosen as surrogates for post-operative complications, indicated that patients had grossly similar post-operative courses in both eras despite the increased use of biologics in the second era. Similarly, some studies have reported no difference in post-operative hospitalizations in patients who were on preoperative biologics compared to patients who had not received them (77, 80, 81).

Strengths and weaknesses

One of the strengths of this study is its use of a large population-based cohort of UC patients with a long follow-up period. In our study, UC was defined using a validated administrative database definition by Rezaie *et al*. (70). This stringent definition was validated using endoscopic and patient chart data (70). In addition, a washout period of a year was used to limit entry into the cohort to incident cases or patients with stable disease that did not require medical attention for the year prior to becoming an index case. Thus, patients with active disease who already had a diagnosis of UC in the year preceding the index date would be excluded. Due to the universal healthcare system in Quebec, all colectomies for UC are captured within this database. Thus, the incidence rate of colectomies for UC could be assessed. In addition, 2005 was chosen as a cut-off to define a pre-biologics and a biologics era as it coincides with the FDA and Health Canada approval for the use of biologics in UC. Furthermore, this cut-off was confirmed as the appropriate demarcation by minimal use of biologics preceding this year. Thus, our study allowed a comparison of two separate population-based cohorts of UC before and after the introduction of biologics in Quebec. In addition, this study design was chosen rather than comparing biologics users and non-users to avoid selection bias, as patients on biologics had to have failed other medical interventions, and were likely at higher risk for a colectomy. However, it remains that a weakness of working with such a database was the inability to accurately assess the severity and duration of UC. Although variables that could be surrogates for markers of severity of disease such as anemia and GI hospitalizations were similar, specific information on extent and complexity of the disease as well as markers of malnutrition and frailty were difficult to capture from such an administrative database. Lastly, we cannot exclude the possibility of residual confounding due to unavailable or unmeasured variables impacting our results. Indeed, as the only

available medication usage data is present for patients on a public medication insurance plan, and this represents the minority of the working population in Québec, analyses were not adjusted for medication usage. Moreover, analyses were not adjusted for disease severity that has been shown to be a predictor of colectomy (82). Also, improvement in IBD patient care over time may have impacted our results and could not be assessed in our study. Improvements in surgical and medical care may have resulted in earlier diagnosis, treatment, and referral to specialized IBD centers. Pre-operative nutritional optimization and advances in minimally invasive techniques may have contributed to the decreased mortality and post-operative outcomes observed in the biologics era (83-85).

Unanswered questions and future directions:

Though the incidence rate of colectomies in the biologics era has decreased, it remains unknown whether the incidence of dysplasia/neoplasia, a long-term consequence of IBD has changed. As it is believed that the development of cancer in UC is driven by the chronic inflammatory changes, long-term follow up studies will better evaluate if the incidence rate of cancer will increase due to the decrease and/or delay in surgical interventions. Another important question that remains undetermined is whether quality of life for UC patients has improved in the biologics era.

Conclusions

In this study, we observed decreased incidence rates of colectomy after the introduction of biologics in Québec. The biologics era was also characterized by decreased post-operative mortality. Future studies with longer follow-ups looking at trends of surgical indications are

necessary to better characterize the role of surgery in patients with UC in the era of salvage medical therapy on the short and long term.

Table 2.1- Logistic regression model comparing patient characteristics in the pre-biologics and biologics eras

	Pre-biologics (N= 2,829)	Biologics (N= 3,313)	OR [95%CI]
Patient demographics			
Mean Age (years) ± SD	48.82 ± 17.53	50.66 ± 17.53	1.01 [1.00-1.01]
Male, n (%)	1,461 (51.64)	1,619 (48.85)	0.90 [0.81-1.00]
Covered, n (%)	1,172 (41.43)	1,375 (41.50)	0.87 [0.77-0.98]
Medical comorbidities, n (%)			
Hypertension	522 (18.45)	732 (22.09)	1.15 [0.98-1.33]
Diabetes	209 (7.39)	358 (10.81)	1.50 [1.23-1.83]
Ischemic heart disease	330 (11.67)	329 (9.92)	0.69 [0.57-0.85]
Congestive heart failure	78 (2.76)	74 (2.23)	0.69 [0.48-1.00]
Cardiovascular disease	92 (3.25)	86 (2.60)	0.74 [0.54-1.03]
Atrial fibrillation	79 (27.93)	117 (35.32)	1.38 [0.99-1.9]
Peptic ulcer disease	84 (2.97)	61 (1.84)	0.61 [0.43-0.87]
Cancer	197 (6.96)	281 (8.48)	1.16[0.95-1.43]

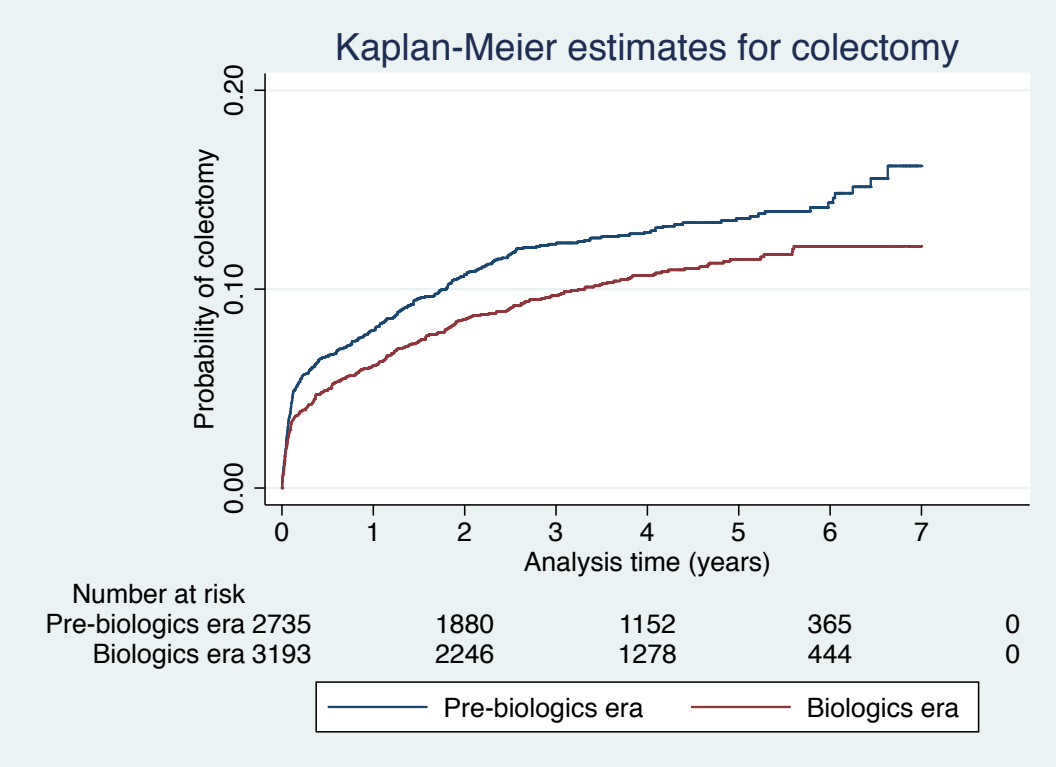

Figure 2.1 Kaplan-Meier estimates for colectomy in pre-biologics and biologics era

Table 2.2: Cox PH regression model: analysis of primary outcome (colectomy)

	Univariate Analysis		Multivariate Analysis	
	HR [95%CI]	***p***	**HR [95%CI]**	***p***
Economic status				
High	1 (reference)	-	*	*
Moderate	1.03 [0.83-1.29]	0.762		
Low	1.05 [0.84-1.31]	0.661		
Social markers				
High	1 (reference)	-	*	*
Moderate	1.07 [0.86-1.32]	0.556		
Low	1.00 [0.80-1.24]	0.993		
Atrial fibrillation	0.98 [0.60-1.58]	0.928	*	*
Cancer	0.83 [0.60-1.14]	0.249	*	*
Peptic ulcer disease	1.25 [0.79-1.98]	0.332	*	*
Cardiovascular disease	0.70 [0.40-1.24]	0.226	*	*
Hypertension	0.95 [0.78-1.16]	0.591	*	*
Gender	1.42 [1.22-1.67]	<0.001	1.47 [1.26-1.72]	<0.001
GI hospitalization	1.35 [1.15-1.58]	<0.001	1.24 [1.04-1.47]	0.015
Congestive heart failure	1.54 [0.99-2.41]	0.057	2.08 [1.27-3.40]	0.004
Age at index date	0.99 [0.99-1.00]	0.018	1.00 [0.99-1.00]	0.068
Urban residence	0.85 [0.71-1.03]	0.098	0.87 [0.72-1.05]	0.146
Ischemic heart disease	0.75 [0.56-1.00]	0.053	0.62 [0.45-0.87]	0.005
Diabetes	0.66 [0.48-0.91]	0.011	0.64 [0.46-0.90]	0.009
Anemia	1.66 [1.40-1.98]	<0.001	1.66 [1.38-2.01]	<0.001
Biologics era	0.80 [0.68-0.93]	0.004	0.81 [0.70-0.95]	0.008

* Variables were not significant and were removed from the final model

GI= gastrointestinal

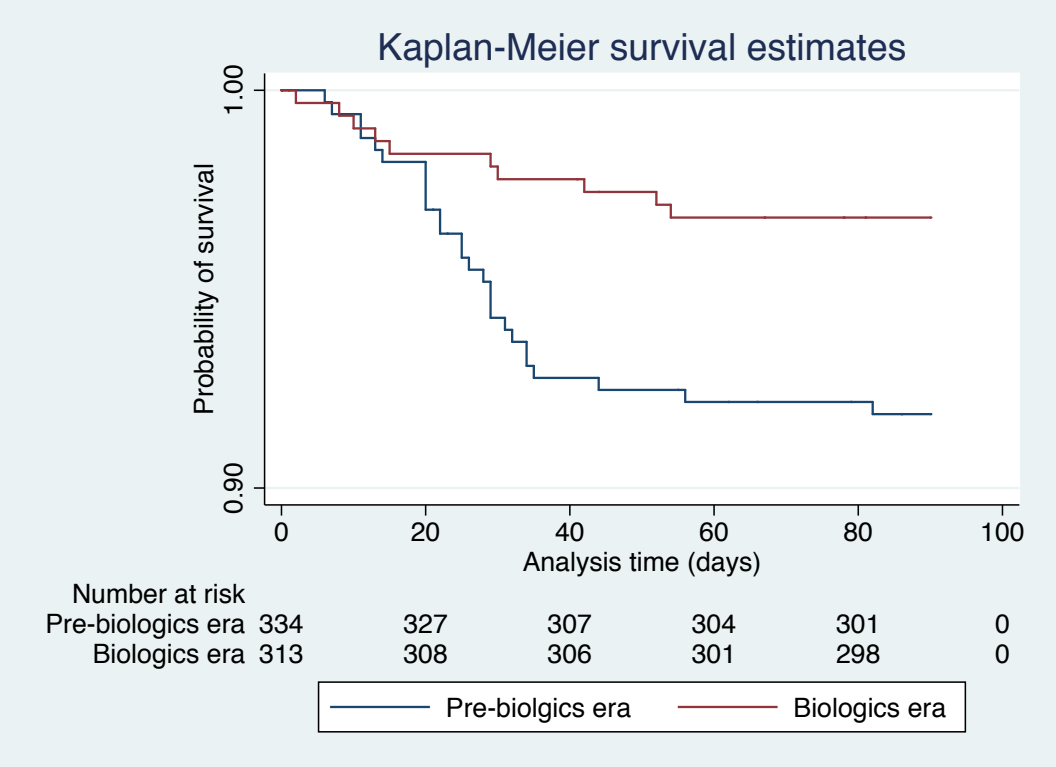

Figure 2.2- Kaplan Meier survival curve for patients in the pre-biologics and biologics era

Table 2.3: Cox PH regression model: analysis of secondary outcome (death up to 90 days post-operatively)

	Univariate Analysis		Multivariate Analysis	
	HR [95%CI]	***p***	**HR [95%CI]**	***p***
Social markers				
High	1 (reference)	-	*	*
Moderate	1.65 [0.54-5.00]	0.379		
Low	2.43 [0.82-7.19]	0.108		
Economic status				
High	1 (reference)	-	*	*
Moderate	0.93 [0.35-2.48]	0.885		
Low	1.47 [0.58-3.70]	0.414		
Atrial fibrillation	10.03 [4.40-22.85]	<0.001	2.26 [0.88-5.79]	0.089
Cancer	6.57 [3.18-13.58]	<0.001	1.96 [0.87-4.43]	0.103
Peptic ulcer disease	1.99 [1.48-8.26]	0.345	*	*
Cardiovascular disease	1.54 [0.21-11.25]	0.669	*	*
Hypertension	5.03 [2.64-9.58]	<0.001	0.85 [0.41-1.78]	0.669
Gender	0.73 [0.39-1.40]	0.348	*	*
GI hospitalization	12.84 [3.09-53.37]	<0.001	5.41 [1.22-23.91]	0.0.026
Congestive heart failure	6.96 [2.90-16.68]	<0.001	0.77 [0.28-2.11]	0.611
Age at index date	1.11 [1.08-1.14]	<0.001	1.08 [1.05-1.12]	<0.001
Urban residence	0.87 [0.41-1.85]	0.725	*	*
Ischemic heart disease	10.95 [5.71-20.99]	<0.001	1.73 [0.81-3.71]	0.158
Diabetes	1.96 [0.69-5.53]	0.204	*	*
Anemia	4.23 [2.19-8.15]	<0.001	1.80 [0.90-3.59]	0.095
Biologics era	0.38 [0.19-0.79]	0.010	0.43 [0.20-0.92]	0.029

*Variables were not significant and were removed from the final model

GI= gastrointestinal

Appendix 1

Physician claims *	Procedure description
5233	Total proctocolectomy
5234	Total proctocolectomy with two surgeons, abdominal surgeon billing code
5166	Total colectomy with end ileostomy or mucous fistula
5232	Colectomy with ileorectal anastomosis
5279	Total colectomy with ileal pouch anastomosis +/- diverting loop ileostomy
5280	Total colectomy with ileal pouch anastomosis +/- diverting loop ileostomy with two surgeons, abdominal surgeon billing code

* Obtained from:
http://www.ramq.gouv.qc.ca/SiteCollectionDocuments/professionnels/manuels/150-facturation-specialistes/000_complet_acte_spec.pdf

Appendix 2: ICD-9 and ICD-10 codes for gastrointestinal hospitalizations

	ICD-9*	ICD-10*
Diseases of the digestive system	520-579	K00-K93
Intestinal infections	009	A09
Neoplasms of oesophagus-anus	150-154	C15-C21
Malignant neoplasm of other ill-defined sites of the digestive organs		C26.0, C26.8, C26.9
Malignant carcinoid tumors of the small intestine	209.0, 209.1, 209.23	
Screening for malignant neoplasm	V76.5	
Secondary malignant neoplasm of intestinte	197.4, 197.5	C78.4, C78.5, C78.8
Carcinoma in situ of digestive organs	230.1-230.7, 230.9	D00.1, D00.2, D01.0-D01.4, D01.7, D01.9
Neoplasm of unknown behaviour in the digestive system	159.0, 159.8, 159.9	D37.1-D37.5, D37.7, D37.9
Benign neoplasm in the digestive system	209.4, 209.5 211.0-211.4	D12, D13.0-D13.3, D13.9
Symptoms and signs involving the digestive system	787, 789.0, 789.7, 789.9	R10-R19
Injury to the intestine, rectum	863.2-863.5	S36.4, S36.5, S36.6
Abnormal radiology findings, abnormal stool or gastrointestinal tissues	793.4, 792.1	R85, R93.3
Artificial opening (gastrostomy, ileostomy, colostomy, other)	V44.1-v44.4 V55.1-v55.4	Z93.1, Z93.2, Z93.3, Z93.4
Intestinal transplant	966.87, V42.84	Z94.81

ICD= International Classification of Disease, IDC-9 refers to the 9th revision and ICD-10 to the 10th revision

Appendix 3- Definitions of medical comorbidities

	ICD-9 *	**ICD-10***
Hypertension	401-405	I10-I15
Diabetes	250	E10-E14
Ischemic Heart Disease	410-414	I20-I25
Peptic Ulcer disease	531-534	K25-K28
Cerebrovascular disease	430-438	I6
Atrial fibrillation	4273	I48
Anemia	28	D5-D8
Cancer	14-19, 200-208	C0-C8, C90-96

* ICD= International Classification of Disease, IDC-9 refers to the 9th revision and ICD-10 to the 10th revision

Connecting text

The patients included in our study had at least one day of drug coverage by the RAMQ anytime between January 1, 1997 and March 31, 2012. This restriction was imposed by RAMQ to limit our sample size for confidentiality purposes. However, our cohort was not restricted to those patients who had public drug insurance for an extended period prior to their index date to allow assessment of prior medication use. Limiting the analysis to patients who had this extended period (e.g. one year) of uninterrupted RAMQ drug coverage would have significantly decreased our sample size. Therefore, prior use of pertinent medications was not assessed in our study and the analyses presented in Chapter 2 were not adjusted for these variables. However, given the importance of medication usage in the prevention of colectomy, we performed a sub-group analysis in patients who were covered by the RAMQ drug insurance plan for at least one year prior to their index date- this data is presented in Chapter 3. We analyzed prior medication (Non-steroidal anti-inflammatory drugs, anti-coagulants, anti-diabetics, anti-hypertensives, corticosteroids, immunomodulators and anti-TNFα agents) in these patients and repeated the analysis presented in chapter 2 for the primary outcome colectomy, after adjusting for these variables.

Chapter 3. Supplementary Analyses: Patients Covered by the Public Prescription Drug Insurance Plan

Information on prescription medications is only available through the RAMQ database for patients who were covered under the public prescription drug insurance plan. From our study cohort, we identified patients who had at least one year of uninterrupted drug coverage by the RAMQ prior to their index date (covered patients) and repeated the analysis for the outcome colectomy in these patients. Medication use was defined for covered patients using pharmaceutical billing codes for filled prescriptions in the year preceding patients' index date. Logistic regression models with backward selection were fitted to characterize patients' baseline characteristics and medication usage. Survival analyses were performed using Kaplan-Meier curves and Cox proportional hazards (PH) models were constructed for the outcome colectomy in this specific subset of patients.

Of the 2,829 patients in the pre-biologics era analyzed in Chapter 2, 1,172 patients were covered by the public drug insurance plan for at least one year prior to their index date compared to 1,375 patients out of the 3,313 patients in the biologics era.

Table 3.1 presents results for the logistic regression model comparing the same patient baseline characteristics as Table 2.1 from Chapter 2. Amongst variables retained in the final model, patients in the pre-biologics era had a lower proportion of hypertension, diabetes and atrial fibrillation but higher proportion of ischemic heart disease and peptic ulcer disease compared to

patients in the biologics era. These results were similar to baseline patient characteristics of the entire cohort presented in Chapter 2, with the exception of age. In fact, the mean age in patients who were covered by the public plan was higher in patients who were covered for a year by the public insurance plan compared to patients who were not necessarily covered for a full year by the public insurance plan (59.53 vs. 42.93, $p< 0.001$).

As evidenced by the Kaplan-Meier curve in Figure 3.1, the unadjusted probability of colectomy was higher in patients in the pre-biologics compared to the biologics era (log rank, p=0.013). The incidence rate of colectomy in patients in the pre-biologics era was 38.18/1000 person-years compared to 28.15/1000 person-years in the biologics era and using Figure 3.2 we obtained 5-year colectomy rates of 14% and 12% for the pre biologics and biologics eras respectively. The 5-year colectomy rates are the same as those reported in Chapter 2 and the incidence rates compare to the incidence rates obtained in Chapter 2 (36.08/1000 person years in the pre-biologics era and 29.99/1000 person years in the post-biologics era).

Use of corticosteroids was similar in both the pre-biologics and biologics eras (31.4% vs. 32.36%, p=0.602). Likewise, use of immunomodulators was similar in both the pre-biologics and biologics eras (32.43% vs. 24.73%, p=0.244). There were no patients with anti-TNFα usage in the pre-biologics era and 11 (0.8%) in the biologics era (p=0.002). A logistic regression model with backward selection was fitted to characterize patients' baseline characteristics and medication usage (Table 3.2). Results of the Cox PH regression model adjusted for medication use are presented in Table 3.3. Use of anti-diabetic medications was associated with a decreased

hazard of colectomy (Hazard ratio, HR; 95%CI 0.51; 0.29-0.90). Use of non-steriodal anti-inflammatory drugs (NSAIDs) was also found be associated with a decreased hazard of colectomy (0.71; 0.52-0.97). However, use of anti-TNFα increased the hazard of colectomy (3.91; 1.24-12.31). After adjusting for patient baseline characteristics and medication use, the biologics era was still associated with a decreased hazard of colectomy (0.73; 0.57-0.93).

In these additional analyses pertaining to patients who were covered under the public drug insurance plan for a year prior to their index date, having received anti-TNFα increased the hazard of colectomy. This result is not surprising as anti-TNFα are prescribed for moderate to severe UC patients who had failed other medical treatments and thus are at higher risk of colectomy. Results of this analysis adjusted for prior medication use were similar to those found in Chapter 2, which indicates that prior medication use did not confound our main results presented in Chapter 2 with regards to the outcome colectomy.

Given that anti-TNFα use was very low among covered patients even in the biologics era, care must be taken when interpreting these results, as they do not represent the totality of patients on biologic agents in the biologics era.

Table 3.1- Covered patients' baseline characteristics, n (%)			
	1998-2004 (N= 2,829)	**2005-2011 (N= 3,313)**	**OR [95%CI]**
Patient demographics			
Male gender	581 (49.57)	617 (44.87)	0.88 [0.75-1.04]
Urban residence	892 (476.11)	1,375 (41.50)	1.16 [0.96-1.40]
Medical comorbidities			
Hypertension	367 (31.31)	501 (36.43)	1.34 [1.10-1.62]
Diabetes	154 (13.13)	229 (16.65)	1.32 [1.03-1.68]
Ischemic heart disease	269 (22.95)	237 (17.23)	0.61 [0.49-0.77]
Atrial fibrillation	71 (6.06))	102 (7.42)	1.34 [1.10-1.62]
Peptic ulcer disease	47 (4.01)	34 (2.47)	0.61 [0.43-0.87]
GI hospitalizations	501 (55.85)	874 (52.97)	0.86 [0.72-1.02]

GI=gastrointestinal

Table 3.2- Patient demographics, hospitalizations and medication use in both eras, n (%)

	Pre-biologics (N= 1,172)	Biologics (N= 1,375)	OR [95%CI]
Male	581 (49.57)	617 (44.87)	0.82 [0.70-0.96]
Urban residence	892 (76.11)	1,375 (78.84)	1.15 [0.95-1.40]
GI hospitalizations	501 (55.85)	874 (52.97)	0.85 [0.71-1.01]
Antihypertensives	507 (43.25)	658 (47.85)	1.18 [1.00-1.41]
Antidiabetics	111 (9.47)	166 (12.07)	1.22 [0.93-1.62]
Anticoagulants	60 (5.12)	94 (6.84)	1.32 [0.92-1.88]
NSAIDs	332 (28.33)	305 (22.18)	0.70 [0.58-0.84]

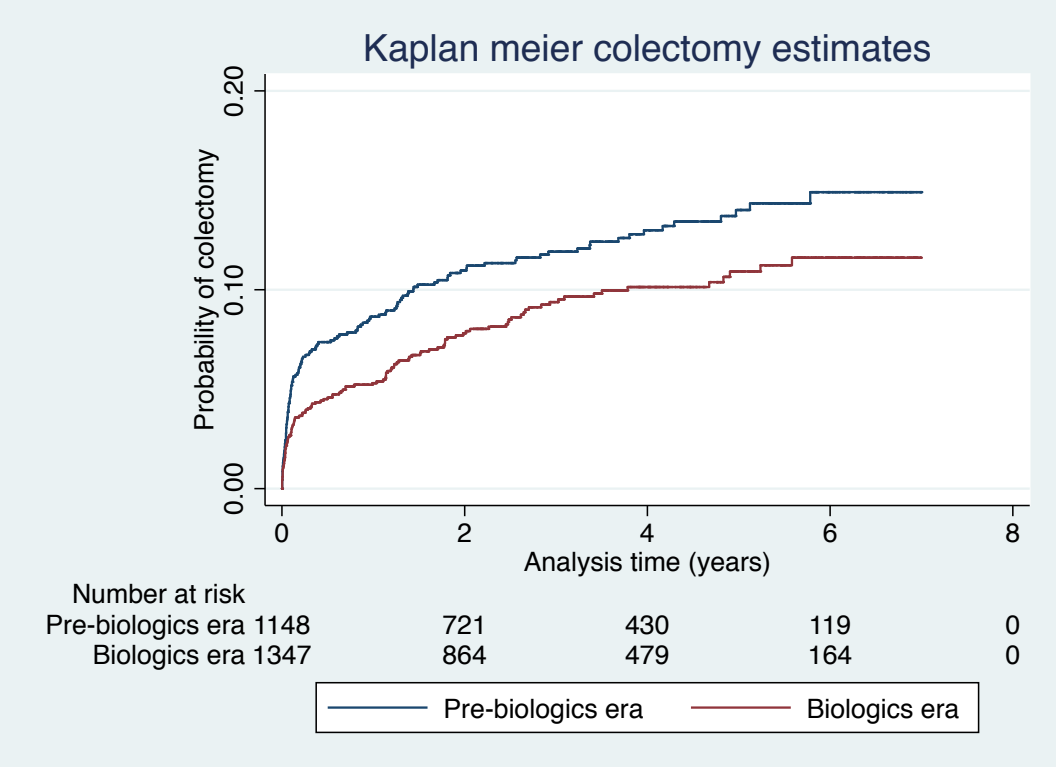

Figure 3.1 Kaplan-Meier estimates for colectomy for covered patients in the pre-biologics and biologics era

Table 3.3: Cox PH regression model: analysis of colectomy in covered patients

	Univariate Analysis		Multivariate Analysis	
	HR [95%CI]	**p**	**HR [95%CI]**	**p**
Social markers				
High	1 (reference)	-	*	*
Moderate	1.27 [0.86-1.87]	0.231		
Low	1.23 [0.85-1.80]	0.284		
Economic status				
High	1 (reference)	-	*	*
Moderate	1.19 [080-1.77]	0.388		
Low	1.18 [0.80-1.74]	0.405		
Cancer	0.78[0.51-1.19]	0.250	*	*
Immunomodulators	1.56 [0.85-2.86]	0.147		
Corticosteroids	1.18 [0.91-1.52]	0.206	*	*
Anti-hypertensives	0.74 [0.57-0.95]	0.018	1.04 [0.76-1.43]	0.804
Gender	1.20 [0.94-1.54]	0.140		
GI hospitalization	1.21 [0.93-1.56]	0.156		
Anti-diabetics	0.45 [0.26-0.79]	0.005	0.51 [0.29-0.90]	0.020
Age at index date	0.99 [0.98-1.00]	0.001	0.99 [0.98-1.00]	0.054
Urban residence	0.84 [0.63-1.10]	0.212		
Anticoagulant	0.39 [0.17-0.87]	0.021	0.47 [0.21-1.07]	0.071
Anti-TNFa	3.24 [1.03-10.11]	0.043	3.91 [1.24-12.31]	0.020
NSAIDs	0.71 [0.52-0.97]	0.032	0.71 [0.52-0.97]	0.03
Biologics era	0.73 [0.57-0.94]	0.013	0.73 [0.57-0.93]	0.011

* Variables were not significant and were removed from the final model
GI= gastrointestinal
NSAIDs= Non-Steroidal Anti-Inflammatory agents

Chapter 4- Discussion

Overall, our results demonstrated a positive impact of the biologics era on a population level in Québec pertaining to decreased rates of colectomies and decreased post-operative mortality. Previously published reports demonstrated decreasing rates of colectomy for patients with UC over time, with conflicting evidence on the role of biologics in further decreasing the rates of colectomies.

Our analyses were limited by the absence of medication data for the proportion of patients who were not covered by the public drug insurance plan in Québec. However, when evaluating patients who were covered by the public drug health insurance plan for a year preceding their index date, we observed similar trends in colectomies as compared to the entire cohort. Moreover, after adjusting for age at cohort entry and medication use including non-steroidal anti-inflammatory drugs, anticoagulants, anti-diabetics and anti-hypertensives, we found that the pre-biologics era and anti-TNFα use were predictors of colectomy on multivariate Cox PH model. However, less than 1% of patients covered in the biologics era had received anti-TNFα prior to their surgery. Given the large amount of missing medication data regarding patients covered by private drug insurance plans, these results should be interpreted with caution. This significant decrease in risk of colectomy in the biologics compared to the pre-biologics era raises some questions on the role of surgical interventions.

Surgery for UC has shifted from occupying a central role in the management of the disease to an option of "last resort", only being considered after medical rescue therapies have failed, or

in the case of development of complications of UC such as fulminant colitis or cancer. As discussed earlier in this thesis, there remains considerable literature questioning the role of recent medical advancements in preventing versus delaying surgery in a subset of patients, especially those with severe disease. At the forefront of the debate in delay of surgical management for UC is the concern that delaying surgery can lead to increased post-operative complications. In 2010, Randall *et al.* published results from a prospectively maintained database from 1994 to 2000 and reported that patients with major post-operative complications had a significantly longer duration of pre-operative medical therapy (86). Although these patients were not on biologics, this study underlined the importance of early surgical interventions in some patients, and the lack of reliable risk factors in identifying patients who will fail rescue therapies and eventually need surgery. A delay in surgical intervention and escalation of medical rescue therapy due to unresponsive disease can result in malnutrition and anemia, thus impacting surgical outcomes. Consequently, it is paramount to identify early predictors of failure of medical management to prevent delays in surgery. Moreover, future research should investigate patients' quality of life with a protracted long course of escalating medical management compared to surgical management. This should be especially considered in view of advancements in surgical techniques with the advantages of minimally invasive surgery and improved pouch outcomes (35).

Another avenue of future research includes the risk of biologics on post-operative outcomes. There remains clinical equipoise on the effects of these agents on post-operative outcomes, and although many studies have attempted to investigate this, they have shown conflicting results. Biologics have a potent role in inhibiting the inflammatory cascade involved in the

healing process. Looking specifically at post-IPAA surgery, a recently published systematic review and meta-analysis reported a significant increase in post-IPAA complications in patients who received pre-operative biologics (OR=4.57 [2.73-7.66]) (87). Moreover, the authors reported a higher risk of pouch-related complications after ileostomy closure in patients on pre-operative biologics (OR=2.27 [1.27-4.05]) and a trend toward higher risk of pouchitis at 1-year follow up (OR=2.01 [0.99-4.07]). However, to this day no large prospective trials have been published to accurately adjust for confounders. Future research is needed to better describe the effect of biologics on post-operative outcomes accounting for disease activity, patient's medications and dosages as well as predictors of post-operative complications.

Moreover, mucosal healing (MH) has recently been recognized as an important treatment target that has the potential to improve outcomes including a decreased risk of colectomy, hospitalization and escalation of medical management (88). Given the data supporting MH as an important predictor of disease outcome, future research should strive to better assess the impact of biologics on MH, and how this will translate into patient-related outcomes. Future long-term data will better elucidate the effects of decreased rates of surgery seen in this study on the incidence of colorectal cancer in relation to MH, especially in evaluating how the introduction of biologics and the decreased rates of surgery have affected the risk and severity of colorectal cancer.

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