RISK COMMUNICATION FOR PATIENTS WITH CHRONIC DISEASE UTILIZING INFLAMMATORY BOWEL DISEASE (IBD) AS A MODEL

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ABSTRACT

Risk Communication for Patients with Chronic Disease Utilizing Inflammatory Bowel Disease (IBD) as a Chronic Disease Model

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Inflammatory bowel disease (IBD) is a group of gastrointestinal disorders that result in significant morbidity and potential mortality among those afflicted. IBD typically requires lifelong care for adequate disease management, and evidence has shown that patients with IBD with poorly controlled disease are at the highest risk for serious and often irreversible negative outcomes including death. IBD pharmacotherapy carries risk of adverse effects, and fear and/or a lack of understanding of benefits and risks associated with treatment options contribute to non-adherence to medical therapy by IBD patients. In addition, although published literature provides some information regarding the risks associated with therapeutic options and from underlying disease, the evidence is often

unclear and there is no consolidated source for providers to use when discussing risk from therapy or disease with patients. The overall aims of this body of work are to quantify the relative risks of serious infection associated with different IBD therapies, as well as to enumerate the risk of cancer inherent to IBD. These are two of the most clinically significant risks associated with IBD and its treatment. In addition, we determine the educational needs of these patients and their providers associated with these risks, in order to inform development of tools to enhance patients' understanding of the risks associated with IBD and its treatment.

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CHAPTER 1: INTRODUCTION

Background

Inflammatory Bowel Disease (IBD)

Inflammatory Bowel Disease is (IBD) is a term used to reference a group of gastrointestinal disorders, most commonly Crohn's disease (CD) and ulcerative colitis (UC). CD and UC are chronic autoimmune conditions characterized by inflammation of the GI tract that result in persistent diarrhea, abdominal pain, malnutrition, abdominal cramping, rectal bleeding, and fatigue. Patients with IBD also experience extraintestinal manifestations such as arthritis, aphthous stomatitis, fistulas, and skin lesions. CD creates inflammation anywhere in the gastrointestinal tract while UC's effects are limited to the colon and rectum. IBD patients often require surgical intervention for disease complications such as intestinal obstructions and fistulas. In addition, CD and UC increase the risk of colorectal cancer as well as cancers from other sites, and contribute to significant morbidity and mortality in this patient population. According to the US Centers for Disease Control and Prevention (CDC), approximately 1.4 million persons in the United States have IBD, many of them teenagers and young adults.[1]

The exact etiology of IBD is not known; however it is hypothesized to develop through interactions between genetic predisposition and environmental factors such as smoking.[2,3] IBD is more prevalent in developed countries as opposed to developing countries, and in urban areas compared to rural areas. This disparity has been attributed to differences in diet, smoking, and exposure to environmental contaminants.[2,3]

IBD Therapy

IBD typically requires lifelong care for adequate disease management. Medical therapies for IBD include anti-inflammatories, antibiotics, corticosteroids, immunomodulators, and biologic medications (please see sidebar), all of which may be used alone or in combination. Biologic medications are synthesized from a living organism or from a living organism's byproducts. The commonly used biologics for the treatment of IBD include: infliximab (Remicade®), certolizumab pegol (Cimzia®), adalimumab (Humira®), and golimumab (Simponi®). These biologics target Tumor Necrosis Factor (TNF) which is a pro-inflammatory cytokine thought to be one biologic pathway involved with the chronic inflammation associated with IBD.[4-8] Natalizumab (Tysabri ®) and vedolizumab are other biologic medications available for the treatment of IBD; however these agents do not target TNF, but instead are humanized monoclonal IgG4 antibodies that are directed against alpha-4 integrin.[4,5,9,10] In addition to the most commonly utilized biologics, newer medications with alternate biological targets are being prescribed more frequently for IBD patients who fail other therapies (e.g. vedolizumab, golimumab, ustekinumab).[11]

Medication Name	Therapeutic Class
Infliximab	Biologic
Adalimumab	Biologic
Certolizumab pegol	Biologic
Golimumab	Biologic
Natalizumab	Biologic
Vedolizumab	Biologic
Ustekinumab	Biologic
Azathioprine	Immunomodulator
6-mercaptopurine	Immunomodulator
Methotrexate	Immunomodulator
Tacrolimus	Immunomodulator
Mycophenolate mofetil	Immunomodulator
Prednisone	Corticosteroid
Budesonide	Corticosteroid
5-aminosalicylate	Anti-inflammatory

Despite the availability of medical therapy, surgical intervention is often required for patients with either CD or UC who do not have adequate response to medical therapy. Unfortunately, surgery is considered curative only for patients with UC due to the disease being limited to the colon.[1] For patients with CD, approximately 70% require surgery due to disease complications arising from failure of medical therapy, and 30% of patients who undergo surgery will experience disease recurrence within three years.[12,13]

Non-adherence to treatment

Each treatment strategy (surgical or medical) carries risk of adverse effects and may not adequately manage the patient's disease. Corticosteroids, immunomodulators, and biologic medications in particular can have significant adverse effects including predisposition to infections and malignancy. In addition, evidence suggests that medical therapy is either unsuccessful or complications develop in 25-33% of patients with UC.[14] Furthermore, patients may elect to forego medical and/or surgical therapy due to inconvenience, cost of therapy, lack of understanding, or fear of side effects from therapy, leading to inadequate disease control and complications. A 2004 meta-analysis estimated that the average non-adherence rate for any indication and any medication is approximately 24.8%.[15] In addition, a 2003 study investigating predictors of non-adherence to medication in a small US IBD patient population estimated a non-adherence rate of 41.2%.[16] Many IBD therapies require dosing multiple times per day (anti-inflammatories, antibiotics, and corticosteroids), are administered via injection (biologics), or are intravenously administered over several hours at an infusion center (biologics), contributing to a higher risk for non-adherence to medical therapy. In

addition, IBD therapies are costly. For example, one year of maintenance treatment with a biologic medication costs approximately $20,000.[17] As IBD typically afflicts teenagers and young adults, and non-adherence to medical therapy is a significant issue specifically for this age group, the average non-adherence rate among this subset of IBD patients may be even higher than 41.2%.[18]

Outcomes from poorly managed IBD

Evidence has shown that patients with IBD with poorly controlled disease are at the highest risk for serious and often irreversible negative outcomes including death.[19-23] One of the most significant negative outcomes is the development of colorectal cancer (CRC). This relationship has been recognized since the 1920s and accounts for an estimated 10-15% of deaths in patients with IBD.[29] It is believed that the risk conferred by IBD is due to the presence of chronic inflammation combined with genetic factors.[29-37] Studies from the published literature over the past five years (2009-2014) have demonstrated that:[38-111]

1. Persistent inflammation in IBD is associated with an increased risk of CRC as previously known.

2. CRC incidence in UC and CD is similar and overall relatively low; however the incidence is higher than that of the general population. Certain subgroups including those with extensive inflammation, younger age at diagnosis, long duration of disease, comorbid primary sclerosing cholangitis (PSC), and pseudopolyposis are at the highest risk among IBD patients.

3. The prognosis for patients with IBD associated CRC may be worse than that of those with non-IBD associated CRC.

4. New discoveries involving the microbiome, molecular pathways, and genetics are numerous; however additional work is needed to more fully understand how these factors are involved with the development, treatment, and potential prevention of IBD associated CRC.

5. There is conflicting evidence regarding the efficacy of thiopurines and 5-aminosalicylates in the prevention of IBD-associated CRC. In addition, endoscopic surveillance's role (including timing) in the prevention and prognosis of IBD associated CRC remains controversial.

In addition to the established relationship between IBD and CRC, there are concerns about a possible association between IBD and lymphoproliferative disorders (LD), such as lymphoma and leukemia. The prevalence of LD is increasing in developed countries, and IBD patients, especially those who receive treatment with immunomodulators, may be at higher risk.[112-114] Previous estimates of the incidence of lymphoma in IBD are 1/4000-5000 persons in those aged 20-29 years old and 1/300-400 persons in those over 70 years of age.[115] The absolute risk of leukemia in IBD is less clear. Studies from the published literature over the past five years (2009-2014) have demonstrated that:[42,44,57,116-145]

1. There is possibly an increased risk of leukemia associated with IBD; however research is lacking in this area.

2. There is an increased risk of lymphoma in patients with IBD; however the overall risk remains low, and the majority of this risk (if not all) is driven by the use of thiopurines.

3. Anti-TNF agents have not been found to be associated with an increased risk of either LD or leukemia.

Statement of problem

Evidence shows that effective intervention early in a patient's disease course is associated with improved long term outcomes such as avoidance of surgery and long term use of corticosteroids.[24-27] As such, it is vital to ensure that patients with IBD receive appropriate and effective treatment as close to initial diagnosis as possible. Inconvenience and cost of therapy are reasons for non-adherence to treatment, but are difficult to address due to limited mutability of either factor. Fear of adverse effects from

therapy and lack of understanding in regards to treatment options are contributing factors to non-adherence amenable to change. In addition, lack of education related to the importance of appropriate disease management on the risk of cancer development and other negative outcomes are other factors impacting adherence that are modifiable. There is a well-established link in the published literature between provider ability to effectively communicate the importance of treatment and potential side effects and patient adherence to medical therapy.[28] The odds of patient adherence to therapy are estimated as 1.62 times higher when physicians are trained in effective communication skills. Furthermore, it is estimated that there is a 19% higher risk of non-adherence in patients whose provider communicates poorly compared to patients with providers who utilize effective communication techniques.[28] In order for a provider to effectively communicate information related to the risks of medical therapies to patients, the provider must have accurate knowledge of the risks of the therapies, as well as be able to convey this information to the patient in an easily understandable format.

Specific Aims

Although published literature provides information regarding the risks associated with therapeutic options and from underlying disease for patients with Inflammatory Bowel Disease, there is no comprehensive reference available for providers' use when discussing risk from therapy or disease with patients. The specific aims of this project are to facilitate the compilation of risk information associated with IBD therapies and determine the educational needs of IBD patients and providers, in order to inform the future development of an educational resource for providers to utilize in their discussions with patients.

Aim 1: To quantify and describe the risk of infection from all currently available medical therapies for the treatment of IBD in the adult population, obtained from a comprehensive review and network meta-analysis of the existing IBD literature. (Chapter 2)

Aim 2a: To quantify and describe the underlying risk for the development of cancer, specifically colorectal cancer (CRC), leukemia, and lymphoma, in adults with IBD, obtained from a comprehensive review and meta-analysis of the existing IBD literature. This measure will be used for future work directed towards quantifying the incremental increase in risk of CRC, leukemia, and lymphoma from IBD therapy. (Chapter 3)

Aim 2b: To identify risk factors for the development of cancer in adults with IBD from the same IBD literature. (Chapter 3)

Aim 2c: To compare the incidence of cancers in the adult IBD population (as estimated by the meta-analysis completed for Aim 2a) to published estimates of the incidence of cancers in the general world adult population. (Chapter 3)

Aim 3: To determine the educational needs of adult IBD patients and their providers, through structured interviews, in reference to the risks from medical therapy such as infection and the risk of cancer risk inherent to IBD. (Chapter 4)

Impact

The overall aims of this body of work are designed to meet the objective of quantifying risks of serious infection and cancer associated with IBD and its treatment. In addition, we determine the educational needs of these patients and their providers associated with these risks, in order to develop tools to enhance their understanding of the risks associated with IBD and its treatment. Based on the principles of shared decision making, we hypothesize that provision of the best evidence available in regards to treatment strategies for IBD and risk factors inherent to IBD, will facilitate patient treatment decision making, support patients in understanding their disease prognosis, and improve adherence to medical therapy, ultimately improving long term outcomes for patients with IBD.

This dissertation presents the findings from three studies that add clinically relevant information to our current knowledge regarding IBD and its therapies. In addition this work provides a foundation for future work in this area, including further study regarding the risks associated with IBD and IBD pharmacotherapy, as well as the development and validation of educational tools within varied IBD patient populations.

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CHAPTER 2: INFLAMMATORY BOWEL DISEASE (IBD) PHARMACOTHERAPY AND THE RISK OF INFECTION: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

Abstract

Introduction: The magnitude of risk of serious infections due to available medical therapies of inflammatory bowel disease (IBD) remains controversial. We conducted a systematic review and network meta-analysis of the existing IBD literature to estimate the risk of serious infection in adult IBD patients associated with available medical therapies.

Methods: Studies were identified by a literature search of PubMed, Cochrane Library, Medline, Web of Science, Scopus, EMBASE, and ProQuest Dissertations and Theses. Randomized controlled trials comparing IBD medical therapies with no restrictions on language, country of origin, or publication date were included. A network meta-analysis was used to pool direct between treatment comparisons with indirect trial evidence while preserving randomization.

Results: Thirty-nine articles fulfilled the inclusion criteria; one study was excluded from the analysis due to disconnectedness. We found no evidence of increased odds of serious infection in comparisons of the different treatment strategies against each other, including combination therapy with a biologic and immunomodulator compared to biologic monotherapy. Similar results were seen in the comparisons between the newer biologics (e.g. vedolizumab) and the anti-tumor necrosis factor agents.

Discussion: No treatment strategy was found to confer a higher risk of serious infection than another. These findings provide a better understanding of the risk of serious infection from IBD pharmacotherapy in the adult population.

Introduction

Inflammatory bowel disease (IBD) typically requires lifelong medical care for adequate disease management. Medical therapies for IBD include anti-inflammatories such as mesalamine or sulfasalazine, antibiotics, corticosteroids, immunomodulators, and biologic medications, all of which may be used alone or in combination. Each treatment strategy carries the risk of adverse effects and may not adequately manage the patient's disease.

Corticosteroids, immunomodulators, and biologic medications in particular can have significant adverse effects possibly including an increased risk of serious infections such as tuberculosis and histoplasmosis. Previous estimates of the proportion of IBD patients with any infection (not limited to serious) following treatment with these medications range from 0.5-30.0%; however there is inconsistency in the reporting of infectious outcomes in the published literature, making the true incidence of infection difficult to determine.[1] In addition, there is conflicting evidence as to whether combinations of therapies modify the risk for serious infection.[2-5] Furthermore, serious infections in particular are relatively rare, and large cohorts of treated patients are required to determine the incidence for specific medications.[1] Lastly, many of these therapies have never been compared directly to each other in the existing literature.

Understanding the risk for infections associated with IBD pharmacotherapy is a crucial consideration for providers and patients. The aim of this study is to estimate the risk of serious infection from currently available medical therapies in adult IBD patients through a systematic review and network meta-analysis. Unique to this study, we compare the risks of serious infection for the different IBD therapies and combinations

of therapies, even in situations where medications have not been compared in previous studies.

Methods

Literature Search

A detailed literature search was conducted to identify all published and unpublished randomized controlled trials (RCTs) of IBD pharmacotherapies in adult patients. Due to the heterogeneity in treatment and outcome reporting, observational studies (i.e. cohort, case-control) were excluded from this analysis. The classes of medications included in the search were corticosteroids (e.g. budesonide, prednisone); immunomodulators (e.g. azathioprine, 6-mercaptopurine, methotrexate); anti-inflammatories (e.g. mesalamine, sulfasalazine); antibiotics (e.g. rifaximin); and biologics (e.g. infliximab, adalimumab, certolizumab pegol, golimumab, vedolizumab). We searched the PubMed, Cochrane Library, Medline, Web of Science, Scopus, EMBASE, and ProQuest Dissertations and Theses databases. Reference lists of published articles were hand searched for secondary sources, and experts in the field contacted for unpublished data. Furthermore, ClinicalTrials.gov, the WHO International Clinical Trial Registry, and scientific information packets of approved IBD pharmacotherapies were scrutinized for additional information sources. No restrictions on language, country of origin, or publication date were used. The duration of investigational treatment and follow-up were required to be at least six weeks each. Figure 1 outlines the literature search and Supplementary Table 1 details the search strategy employed.

Inclusion and Exclusion Criteria

All RCTs that reported odds ratios (ORs) or provided information sufficient to accurately calculate ORs for serious infection in adult IBD patients were included. Serious infections were defined per the US Food and Drug Administration's guidelines[6] as one that results in death, is life-threatening, results in hospitalization or prolongs hospitalization, causes disability or permanent damage, or is considered by the reporting investigator as an event that requires medical or surgical intervention to avoid one of these specified outcomes. Studies focusing on pediatric populations, those with incomplete reporting of serious adverse events, those without a comparison group (open-label trials), those of treatment duration and length of follow up less than 6 weeks each, and those not written in English and unable to be translated to English were excluded. If publications reported duplicate data on a population, only the publication with the longest follow-up period was included.

Data Collection and Quality Assessment

Two independent reviewers (CW and KCS) examined each article for inclusion according to the eligibility criteria. Any disagreement was resolved through discussion and consensus. Thirty-nine articles fulfilled the inclusion criteria (Figure 1).[4,7-44]

We retrieved demographic (where possible) and outcome data for each included article using standardized forms. Individual studies were assigned a bias risk rating using the Cochrane Collaboration's Risk of Bias Assessment Tool.[45] The strength of evidence for each cancer was assessed utilizing The Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach.[45]

Statistical Analysis

A network meta-analysis (NMA) technique, also known as mixed treatment comparison methods, was used to compare the risk of serious infection associated with different medications used to treat IBD. This methodological framework allowed us to construct a network of interconnected RCTs from which we could make indirect comparisons between treatments in two trials that have one treatment in common, even in situations where treatments have not been directly compared. [46-48] For example, in trial 1 treatment A is compared to treatment B, and in trial 2 treatment B is compared to treatment C. A NMA allows us to make a valid evaluation of treatment A and treatment C although these two therapies were not directly compared in a single study. Through the use of a NMA, we were able to preserve the within trial randomized treatment comparisons, as well as add information from all of the available indirect comparisons between therapies.[46-48]

The logarithm of the odds ratio (OR) for each trial and its standard error (SE) were calculated and used in the network-meta-analysis. Each arm of the individual trials was classified according to its primary treatment strategy. A multivariate random-effects logistic regression model using restricted maximum likelihood (REML) was used to combine estimates. Statistical analysis was performed using Stata SE version 14 (StataCorp, College Station, TX). We performed the NMA using the *network* suite of commands published by White.[49] Graphs were generated using the published Stata routines of Chaimani.[50]

A crucial consideration in any NMA is the evaluation of inconsistency, or incoherence. Indirect evidence can be combined in large samples if the assumption is

made that across treatment comparisons, there are no important differences in the types of studies contributing to the comparisons, or in other words that there is consistency.[51] We assessed inconsistency using a design-by-treatment interaction model, which allows for the global testing for the presence of inconsistency in NMAs with multi-arm studies.[51] Visual assessment of a comparison-adjusted funnel plot was used to assess for the presence of publication bias and other small study effects.[50] P-values of ≤ .05 were considered statistically significant.

Results

Table 1 displays a summary of the trials included in the NMA. One of the identified trials[18] did not fit into the connected network because of its treatment comparators (infliximab+MTX+prednisone and infliximab+prednisone), which were not examined in any of the other included trials; thus this trial was excluded from the analysis. Figure 2 illustrates the network of RCTs by treatment strategy. Each node in the network represents a treatment strategy and the edges signify pairwise treatment comparisons from the trials included. The size of the node corresponds to the number of randomly assigned participants (sample size), with a larger node signifying a larger sample size. The width of connecting lines is proportional to the number of trials comparing each pair of therapies. If there is no line connecting two nodes, no studies directly compared the two treatments.[52]

Table 2 provides the estimated odds of serious infection for all treatment strategies compared to placebo. Amongst all therapy contrasts, no statistically significantly increased odds of serious infection were discovered. However, the confidence intervals were extremely wide in many of the comparisons, and a clinically

significant increase in infection risk could not be excluded. Supplemental Table 2 summarizes the comparisons among each treatment strategy and an aminosalicylate or antibiotic. Table 3 displays the estimates for selected therapeutic strategies compared to the anti-tumor necrosis factor (anti-TNF) biologics including infliximab, adalimumab, and certolizumab pegol. Again, no statistically significant increased odds of serious infection were observed for any treatment comparisons including those between the specific anti-TNFs agents (i.e. adalimumab vs. infliximab), as well as those between anti-TNF monotherapy and dual therapy with an immunomodulator (i.e. infliximab alone vs. infliximab+azathioprine/6MP). Supplemental Table 3 provides an overview of the remaining treatment comparisons with the anti-TNF agents, including golimumab, and again shows no statistically significant differences in the odds of infection between the different treatment strategies.

Furthermore, no statistically significant increased odds of serious infection were found for any comparison in contrasting each therapy with the immunomodulators (azathioprine/6MP and methotrexate) or other commonly used therapies such as prednisone, budesonide, and tacrolimus (Table 4, Supplemental Tables 4 and 5). Similar findings were seen for the newer biologic pharmacotherapies including natalizumab, ustekinumab, and vedolizumab (Table 4, Supplemental Table 6). Lastly, no increased odds of serious of infection were found in comparisons of each included treatment strategy against other combinations of therapies such as methotrexate/prednisone or azathioprine/6MP+prednisone (Supplemental Table 7). However again, the confidence intervals were extremely wide in many of the comparisons, and a clinically significant increase in infection risk could not be excluded.

In the design-by-treatment interaction model, no evidence of inconsistency was found (chi^2=0.25, p=0.9984). Visual assessment of a comparison-adjusted funnel plot did not reveal any evidence of publication bias or other small study effects. Given the randomized nature of the included studies and the low probability of bias, the overall quality of the body of evidence per the GRADE approach is high.

Discussion

In this network meta-analysis (NMA), we combined clinical trial data from thirty-eight published articles that included twenty-four different treatment strategies for IBD. These results summarize the risk of serious infection from available RCTs of commonly prescribed IBD pharmacotherapies. The study overcomes some of the limitations from previous studies by applying a universal definition for serious infection and examining large cohorts of treated patients from RCTs. Furthermore, the NMA technique allows for investigation of multiple therapies, including combinations of therapies, which have not been previously compared directly.

Our results show that no treatment strategy exhibits a higher odds of serious infection than another (including placebo), although in many cases the confidence intervals were wide, likely due to the small number of studies examining specific therapies available, and thus did not exclude a clinically significant increase in risk. Of particular interest, patients treated with dual immunosuppression with biologic medications and immunomodulators do not appear to be at higher risk of serious infection compared to those treated with biologic monotherapy. This lends additional support towards the safety of combination therapy as a viable treatment strategy, especially for those patients who are at high risk of antibody formation and subsequent

loss of response from some biologic therapies. In addition, we found no evidence of a higher odds of serious infection from the newly available biologic therapies, such as vedolizumab and ustekinumab, compared to the anti-tumor necrosis factor (anti-TNF) biologic agents (or to one another). Given the growing number of patients who have lost response or who are intolerant to anti-TNFs, these findings are reassuring. Furthermore, we specifically looked at the comparison of those on triple immunosuppression (i.e. biologic+immunomodulator+steroid) versus those on combination therapy or biologic monotherapy, and similar results were found. Our findings do have some limitations. First, we only included data from RCTs due to the added heterogeneity non-randomized studies would contribute to the analysis, as well as the desire to preserve the benefits of randomization in our analysis. This limits the external validity and representativeness of our findings, especially given the strict entry criteria for these trials. Patients with comorbidities or other characteristics excluded from these studies may be at higher risk of serious infections from IBD pharmacotherapy than those included in our study population. Second, RCTs are not specifically designed or powered to investigate adverse events such as serious infections; thus we may underestimate the true association of these therapies with serious infection, a limitation that is not overcome by pooling evidence in a meta-analysis. Third, there was variable length of treatment and follow up among the included studies, which may underestimate the risk of serious infection. Many of the included trials had short follow-up duration, so longer-terms risks of these therapies were not quantified. Fourth, the direct estimates for some therapeutic strategies are based on a single study due to the lack of available trial data. Lastly, traditional

limitations of meta-analyses due to variations in the treatment regimens, in the study populations, and in the conduct of the individual trials may bias our estimates, the direction of which is indeterminable.

Despite these limitations, this study provides crucial information regarding one of the most clinically significant risks of interest associated with IBD pharmacotherapy. Our findings are robust in terms of the low estimate of inconsistency for our model and the completeness of the literature search of studies for inclusion. As additional data becomes available regarding IBD therapies, this information can be added to the network to increase our confidence in the estimates. Our results add to the body of evidence regarding risks and benefits of IBD pharmacotherapy, and suggest that commonly used therapies are not associated with increased risk of serious infections. Further, long-term studies using larger cohorts will supplement these findings and increase the generalizability of these results.

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Tables and Figures

Table 1: Characteristics of included studies

Author	Journal	Publication Year	Region of Origin	Number of Sites	Study Duration* (wks)	Diagnosis	Treatment Groups	Number of Patients	Mean Age (yrs)	Female (%)	Mean Disease Duration (months)	Surgery (%)	Smoking History (%)	Concomitant Immunomodulator** Use (%)	Concomitant 5-aminosalicylate Use (%)	Concomitant Steroid Use (%)	Observed Number of Serious Infections	Bias Rating
Ardizzone[7]	Dig Liver Dis	2003	Europe (Western)	1	24	CD	MTX+prednisone	27	37.0	51.9	76.6	33.0	NR	0.0	0.0	0.0	0	Low
							AZA+prednisone	27	31.0	44.0	57.3	30.0	NR	0.0	0.0	0.0	0	
Ardizzone[8]	Gut	2006	Europe (Western)	1	24	UC	AZA+prednisone	36	43.0	44.0	64.4	NR	25.0	0.0	0.0	0.0	0	Low
							5-ASA+prednisone	36	45.0	47.0	67.5	NR	17.0	0.0	0.0	0.0	1	
Arora[9]	Hepatogastroenterol	1999	N America	1	52	CD	MTX+prednisone	15	37.3	20.0	109.2	26.7	NR	0.0	NR	0.0	1	Low
							Placebo+prednisone	18	35.6	55.6	140.4	55.6	NR	0.0	NR	0.0	0	
Bar-Meir[10]	Gastroenterology	1998	Middle East	14	8	CD	Budesonide	100	32.7	47.0	60.0	15.0	30.0	0.0	0.0	0.0	0	Low
							Prednisone	101	32.8	49.5	60.0	23.8	31.0	0.0	0.0	0.0	0	
Bar-Meir[11]	Dis Colon Rectum	2003	Worldwide	38	8	UC	Budesonide foam	120	42.0	62.0	42.0	NR	41.0	0.0	52.0	0.0	0	Low
							Hydrocortisone foam	128	42.0	52.0	45.6	NR	30.0	0.0	63.0	0.0	0	
Colombel[12]	Gastroenterology	2007	Worldwide	92	56	CD	Adalimumab	517	NR	61.9	NR	NR	35.6	51.0	39.3	38.9	14	Low
							Placebo	261	NR	62.1	NR	NR	35.6	50.6	39.5	38.7	9	
Colombel[4]	N Engl J Med	2010	Worldwide	92	50	CD	Infliximab	169	35.0	50.3	26.4	NR	NR	0.0	51.5	47.4	8	Low
							AZA	170	35.0	47.1	28.8	NR	NR	0.0	61.2	38.2	9	
							Infliximab+AZA	169	34.0	47.9	26.4	NR	NR	0.0	50.3	39.0	7	
Cortot[13]	Gut	2001	Worldwide	24	22	CD	Budesonide+prednisone	59	35.0	52.5	106.8	30.5	NR	15.3	49.2	0.0	0	Low
							Placebo+prednisone	58	32.0	65.6	97.2	36.2	NR	8.6	48.3	0.0	0	
D'Haens[14]	Lancet	2008	Europe (Western)	18	104	CD	Infliximab+AZA (or MTX)	67	30.0	66.2	2.0	NR	55.4	0.0	4.6	0.0	4	Low
							Prednisone&	66	28.7	57.8	2.5	NR	60.9	0.0	3.1	0.0	7	
Ewe[15]	Gastroenterology	1993	Europe (Western)	1	16	CD	AZA+prednisone	21	27.3	NR	55.2	NR	NR	0.0	57.0	0.0	0	Low
							Placebo+prednisone	21	29.3	NR	46.8	NR	NR	0.0	37.0	0.0	0	

Table 1, cont.: Characteristics of included studies

Author	Journal	Publication Year	Region of Origin	Number of Sites	Study Duration* (wks)	Diagnosis	Treatment Groups	Number of Patients	Mean Age (yrs)	Female (%)	Mean Disease Duration (months)	Surgery (%)	Smoking History (%)	Concomitant Immunomodulator** Use (%)	Concomitant 5-aminosalicylate Use (%)	Concomitant Steroid Use (%)	Observed Number of Serious Infections	Bias Rating
Feagan[16]	N Engl J Med	1995	N America	8	16	CD	MTX+prednisone	94	34.0	46.0	93.0	47.0	49.0	0.0	0.0	0.0	0	Low
							Placebo+prednisone	47	36.0	45.0	98.0	47.0	47.0	0.0	0.0	0.0	0	
Feagan[17]	N Engl J Med	2000	N America	7	40	CD	MTX	40	32.0	60.0	88.0	43.0	50.0	0.0	0.0	0.0	0	Low
							Placebo	36	34.0	39.0	84.0	36.0	42.0	0.0	0.0	0.0	1	
Feagan[18]	Gastroenterology	2014	Canada	15	50	CD	Infliximab+MTX+prednisone	63	40.4	46.6	130.9	57.1	63.5	0.0	0.0	0.0	0	Low
							Infliximab+placebo+prednisone	63	38.5	41.3	115.4	46.0	57.2	0.0	0.0	0.0	0	
Hanauer[19]	Gastroenterology	2004	N America	5	104	CD	6MP	47	34.9	51.0	113.0	100.0	NR	0.0	0.0	0.0	0	Low
							5-ASA	44	34.1	57.0	120.0	100.0	NR	0.0	0.0	0.0	0	
							Placebo	40	34.2	55.0	127.0	100.0	NR	0.0	0.0	0.0	0	
Hawthorne[20]	BMJ	1992	Europe (Western)	5	52	UC	AZA	40	50.0	62.5	NR	NR	NR	0.0	80.0	NR	0	Low
							Placebo	39	40.5	33.3	NR	NR	NR	0.0	85.0	NR	0	
Lemann[21]	Gastroenterology	2006	Europe (Western)	22	52	CD	Infliximab+AZA/6MP+prednisone	57	26.5	52.6	48.0	NR	NR	0.0	0.0	0.0	0	Low
							AZA/6MP+prednisone	56	27.5	57.1	66.0	NR	NR	0.0	0.0	0.0	3	
Mantzaris[22]	Am J Gastroenterol	2004	Europe (Western)	1	104	UC	AZA+5-ASA	36	33.0	50.0	60.0	NR	8.0	0.0	0.0	0.0	0	Low
							AZA	34	35.0	52.9	48.0	NR	6.0	0.0	0.0	0.0	0	
Neurath[23]	Gut	1999	Europe (Western)	1	24	CD	AZA+prednisone	35	NR	NR	NR	NR	NR	0.0	NR	0.0	0	Low
							MMF+prednisone	35	NR	NR	NR	NR	NR	0.0	NR	0.0	0	
Ochsenkun[24]	Gastroenterology	2003	Not reported	Not reported	13	UC	Infliximab	6	NR	NR	NR	NR	NR	NR	NR	NR	0	Uncertain
							Prednisone	7	NR	NR	NR	NR	NR	NR	NR	NR	0	
Odonnell[25]	Gut	1992	Europe (Western)	1	6	UC	5-ASA enemas	24	49.0	28.3	NR	NR	NR	NR	75.0	NR	0	Low
							Prednisone enemas	21	43.0	61.9	NR	NR	NR	NR	71.4	NR	0	

Table 1, cont.: Characteristics of included studies

Author	Journal	Publication Year	Region of Origin	Number of Sites	Study Duration* (wks)	Diagnosis	Treatment Groups	Number of Patients	Mean Age (yrs)	Female (%)	Mean Disease Duration (months)	Surgery (%)	Smoking History (%)	Concomitant Immunomodulator** Use (%)	Concomitant 5-aminosalicylate Use (%)	Concomitant Steroid Use (%)	Observed Number of Serious Infections	Bias Rating
Oren[26]	Gastroenterology	1996	Middle East	12	36	UC	MTX	30	38.3	43.3	95.2	NR	51.7	0.0	66.7	70.0	0	Low
							Placebo	37	38.9	51.4	70.2	NR	51.4	0.0	67.6	73.0	0	
Orth[27]	Am J Gastroenterol	2000	Europe (Western)	1	52	UC	MMF+prednisone	12	42.4	50.0	149.0	0.0	NR	0.0	66.7	0.0	2	Low
							AZA+prednisone	12	40.4	25.0	87.0	0.0	NR	0.0	66.7	0.0	1	
Prantera[28]	Gastroenterology	2012	Worldwide	55	12	CD	Rifaximin	308	33.3	56.8	40.0	28.6	21.8	25.2	67.4	48.8	1	Low
							Placebo	102	37.0	59.0	39.0	32.0	26.0	27.0	71.0	48.0	0	
Present[29]	N Engl J Med	1999	Worldwide	12	34	CD	Infliximab	63	38.1	57.1	151.2	60.3	NR	46.0	52.4	34.9	3	Low
							Placebo	31	35.4	46.0	144.0	59.0	NR	29.0	61.0	35.0	0	
Rutgeerts[30]	Gastroenterology	1995	Europe (Western)	1	12	CD	Metronidazole	30	33.0	NR	108.0	NR	NR	0.0	0.0	NR	0	Low
							Placebo	30	37.0	NR	120.0	NR	NR	0.0	0.0	NR	0	
Rutgeerts[31]	N Engl J Med	2005	Worldwide	62	46	UC	Infliximab	243	42.1	38.3	85.8	NR	46.1	51.4	69.1	58.8	11	Low
							Placebo	121	41.4	40.5	74.4	NR	50.4	43.8	70.2	65.3	5	
				55	22	UC	Infliximab	241	40.4	40.2	79.2	NR	46.9	42.3	75.9	52.3	5	
							Placebo	123	39.3	42.3	78.0	NR	48.8	43.9	72.4	48.8	1	
Rutgeerts[32]	Gastroenterology	2005	Europe (Western)	2	54	CD	Ornidazole	38	35.0	57.9	84.0	100.0	44.7	0.0	0.0	52.3	0	Low
							Placebo	40	30.5	50.0	36.0	100.0	47.5	0.0	0.0	35.0	0	
Sandborn[33]	Gastroenterology	2003	N America	18	10	CD	Tacrolimus	21	40.8	52.4	NR	62.0	33.0	62.0	43.0	24.0	0	Low
							Placebo	25	38.1	66.0	NR	44.0	16.0	14.0	40.0	16.0	0	
Sandborn[34]	N Engl J Med	2005	Worldwide	142	12	CD	Natalizumab	724	38.0	57.0	121.0	41.0	23.0	34.0	47.0	38.0	12	Low
							Placebo	181	39.0	60.0	110.0	40.0	24.0	28.0	44.0	40.0	4	
					48	CD	Natalizumab	168	37.0	54.0	119.0	33.0	16.0	37.0	9.0	38.0	6	
							Placebo	171	37.0	65.0	116.0	40.0	26.0	35.0	54.0	46.0	5	
Sandborn[35]	Gut	2007	Worldwide	53	56	CD	Adalimumab	37	36.0	56.8	101.2	NR	86.5	24.3	70.3	45.9	0	Low
							Placebo	18	36.0	67.0	98.9	NR	67.0	18.0	44.0	56.0	0	

Table 1, cont.: Characteristics of included studies

Author	Journal	Publication Year	Region of Origin	Number of Sites	Study Duration* (wks)	Diagnosis	Treatment Groups	Number of Patients	Mean Age (yrs)	Female (%)	Mean Disease Duration (months)	Surgery (%)	Smoking History (%)	Concomitant Immunomodulator** Use (%)	Concomitant 5-aminosalicylate Use (%)	Concomitant Steroid Use (%)	Observed Number of Serious Infections	Bias Rating
Sandborn[36]	N Engl J Med	2007	Worldwide	171	26	CD	Certolizumab pegol	331	37.0	53.0	84.0	36.0	31.0	21.0	NR	22.0	7	Low
							Placebo	329	38.0	60.0	96.0	34.0	33.0	20.0	NR	23.0	3	
Sandborn[37]	Gastroenterology	2012	Worldwide	103	52	UC	Adalimumab	248	39.6	42.7	97.2	NR	NR	37.5	58.9	60.5	4	Low
							Placebo	246	41.3	38.2	102.0	NR	NR	32.5	63.0	56.9	5	
Sandborn[38]	N Engl J Med	2012	Worldwide	153	36	CD	Ustekinumab	394	38.8	61.2	147.6	NR	NR	24.4	17.0	48.0	10	Low
							Placebo	132	39.5	51.5	148.8	NR	NR	22.7	18.2	55.3	8	
Sandborn[39]	N Engl J Med	2013	Worldwide	285	52	CD	Vedolizumab	967	35.7	53.4	110.4	42.6	27.3	16.1	NR	34.7	45	Low
							Placebo	148	38.6	53.4	98.4	36.5	23.0	16.9	NR	30.4	9	
Sandborn[40]	Gastroenterology	2014	Worldwide	251	52	UC	Golimumab	308	40.3	46.1	84.0	NR	NR	30.8	80.2	53.8	10	Low
							Placebo	156	40.2	51.9	82.8	NR	NR	33.3	80.1	56.4	3	
Sands[41]	Inflamm Bowel Dis	2007	N America	17	32	CD	Natalizumab+infliximab	52	39.9	54.0	150.3	NR	NR	50.0	46.0	27.0	0	Low
							Placebo+infliximab	27	38.9	37.0	120.0	NR	NR	56.0	37.0	30.0	0	
Schreiber[42]	Gastroenterology	2005	Worldwide	58	20	CD	Certolizumab pegol	219	36.5	48.6	99.6	36.1	NR	37.4	44.3	34.7	1	Low
							Placebo	73	35.8	67.1	95.4	37.0	NR	35.6	39.7	39.7	0	
Schreiber[43]	N Engl J Med	2007	Worldwide	147	20	CD	Certolizumab pegol	215	38.0	57.0	108.0	30.0	30.0	27.0	NR	22.0	6	Low
							Placebo	210	38.0	48.0	84.0	35.0	36.0	25.0	NR	21.0	2	
Targan[44]	Gastroenterology	2007	Worldwide	114	8	CD	Natalizumab	259	38.1	59.0	121.4	NR	NR	37.0	49.0	42.0	1	Low
							Placebo	250	37.7	59.0	120.3	NR	NR	38.0	48.0	38.0	4	

Abbreviations: CD=Crohn's Disease; UC=ulcerative colitis; NR=not reported; MTX=methotrexate; AZA=azathioprine; 6MP=6-mercaptopurine; MMF=mycophenolate mofetil

*inclusive of active treatment period and follow-up

**includes MTX, 6MP, AZA

[&]Step-up strategy starting with prednisone then progressing to AZA

Table 2: Estimated odds of serious infection for treatment strategies compared to placebo

Treatment Strategy	Comparator	Odds Ratio	Standard Error	95% Confidence Interval	
Infliximab	Placebo	1.36	0.45	0.57	3.27
Adalimumab	Placebo	0.77	0.36	0.38	1.56
Certolizumab pegol	Placebo	2.37	0.50	0.88	6.38
Natalizumab	Placebo	0.80	0.40	0.37	1.73
Ustekinumab	Placebo	0.40	0.49	0.16	1.05
Vedolizumab	Placebo	0.75	0.38	0.36	1.58
Golimumab	Placebo	1.71	0.67	0.46	6.31
Methotrexate	Placebo	0.52	1.28	0.04	6.34
Azathioprine/6MP	Placebo	1.43	0.61	0.43	4.76
Prednisone	Placebo	1.92	0.85	0.36	10.21
Budesonide	Placebo	1.99	1.65	0.08	50.97
Aminosalicylate	Placebo	1.37	1.40	0.09	21.47
Antibiotic	Placebo	1.01	1.07	0.12	8.34
Tacrolimus	Placebo	1.19	2.02	0.02	62.32
Methotrexate+prednisone	Placebo	2.94	1.45	0.17	50.23
Azathioprine/6MP+prednisone	Placebo	2.37	1.76	0.07	75.25
Aminosalicylate+prednisone	Placebo	7.32	2.41	0.06	832.34
Budesonide+prednisone	Placebo	1.89	2.18	0.03	135.88
MMF+prednisone	Placebo	4.14	2.07	0.07	241.50
Infliximab+azathioprine/6MP	Placebo	1.10	0.65	0.31	3.97
Azathioprine/6MP+aminosalicylate	Placebo	1.35	2.11	0.02	83.66
Natalizumab+inflximab	Placebo	0.71	2.06	0.01	40.65
Infliximab+azathioprine/6MP+prednisone	Placebo	0.32	2.33	0.00	30.40

Abbreviations: 6MP=6-mercaptopurine; MMF=mycophenolate mofetil

Table 3: Estimated odds of serious infection for selected* treatment strategies compared to anti-tumor necrosis factor biologics

Treatment Strategy	Comparator	Odds Ratio	Standard Error	95% Confidence Interval	
Adalimumab	Infliximab	0.57	0.57	0.18	1.74
Certolizumab pegol	Infliximab	1.74	0.67	0.47	6.53
Natalizumab	Infliximab	0.58	0.60	0.18	1.88
Ustekinumab	Infliximab	0.30	0.66	0.08	1.08
Vedolizumab	Infliximab	0.55	0.58	0.18	1.74
Golimumab	Infliximab	1.26	0.80	0.26	6.05
Infliximab+azathioprine/6MP	Infliximab	0.81	0.50	0.30	2.17
Infliximab+azathioprine/6MP+prednisone	Infliximab	0.23	2.29	0.00	20.82
Certolizumab pegol	Adalimumab	3.08	0.62	0.91	10.37
Natalizumab	Adalimumab	1.03	0.54	0.36	2.94
Ustekinumab	Adalimumab	0.52	0.60	0.16	1.71
Vedolizumab	Adalimumab	0.98	0.52	0.35	2.71
Golimumab	Adalimumab	2.22	0.76	0.50	9.78
Natalizumab	Certolizumab pegol	0.34	0.64	0.10	1.18
Ustekinumab	Certolizumab pegol	0.17	0.70	0.04	0.67
Vedolizumab	Certolizumab pegol	0.32	0.63	0.09	1.09
Golimumab	Certolizumab pegol	0.72	0.84	0.14	3.71

Abbreviations: 6MP=6-mercaptopurine; MMF=mycophenolate mofetil

*Other group comparisons can be found in Supplemental Table 3

Table 4: Estimated odds of serious infection for selected* treatment strategies of interest

Treatment Strategy	Comparator	Odds Ratio	Standard Error	95% Confidence Interval	
Azathioprine/6MP	Methotrexate	2.75	1.42	0.17	44.07
Prednisone	Azathioprine/6MP	1.34	0.76	0.30	5.96
Infliximab+azathioprine/6MP	Azathioprine/6MP	0.77	0.50	0.29	2.06
Ustekinumab	Natalizumab	0.51	0.63	0.15	1.73
Vedolizumab	Natalizumab	0.95	0.55	0.32	2.76
Golimumab	Natalizumab	2.15	0.77	0.47	9.82
Vedolizumab	Ustekinumab	1.87	0.61	0.56	6.22
Golimumab	Ustekinumab	4.24	0.82	0.84	21.32
Golimumab	Vedolizumab	2.27	0.76	0.51	10.16

Abbreviations: 6MP=6-mercaptopurine

*Other group comparisons can be found in Supplemental Tables

Supplemental Table 1: Search Algorithms

PUBMED (results returned=323)
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EMBASE (results returned=83)
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SCOPUS (results returned=131)
ALL(inflammatory bowel disease* OR crohn* disease OR colitis OR enterocolitis OR ileitis OR ileocolitis) AND ALL(antibiotics OR mycophenolate mofetil OR MMF OR cellcept OR methotrexate OR amethopterin OR 6-mercaptopurine OR mercaptopurine OR 6MP OR purinethol OR azathioprine OR corticosteroids OR budesonide OR entocort OR methylprednisolone hemisuccinate OR solumedrol OR mesalamine OR aminosalicylic acids OR 5-aminosalicylate OR azulfidine OR sulfasalazine OR asacol OR pentasa OR salofalk OR dipentum OR colazal OR lialda OR apriso OR canasa OR rowasa OR olsalazine OR balsalizide OR natalizumab OR tysabri OR vedolizumab OR ustekinumab OR stelara OR infliximab OR remicade OR certolizumab pegol OR cimzia OR adalimumab OR humira OR golimumab OR simponi OR cyclosporine) AND ALL(bacterial infection OR mycoses OR fungal infection OR viral diseases OR viral infection OR tuberculosis OR histoplasmosis OR coccidioidmycosis)
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WEB OF SCIENCE (results returned=4470)

TS=(inflammatory bowel disease* OR crohn* disease OR ulcerative colitis OR colitis OR enterocolitis OR ileitis OR ileocolitis) AND TS=(antibacterial agents OR antibiotics OR mycophenolate mofetil OR MMF OR cellcept OR antimetabolites OR methotrexate OR amethopterin OR 6-mercaptopurine OR mercaptopurine OR 6MP OR purinethol OR azathioprine OR adrenal cortex hormones OR corticosteroids OR budesonide OR entocort OR methylprednisolone hemisuccinate OR solumedrol OR anti-inflammatory agents OR mesalamine OR aminosalicylic acids OR gastrointestinal agents OR 5-aminosalicylate OR azulfidine OR sulfasalazine OR asacol OR pentasa OR salofalk OR dipentum OR colazal OR lialda OR apriso OR canasa OR rowasa OR olsalazine OR balsalizide OR antibodies, monoclonal OR monoclonal antibodies OR natalizumab OR tysabri OR vedolizumab OR ustekinumab OR stelara OR integrin alpha4 OR tumor necrosis factor alpha OR anti-TNF OR infliximab OR remicade OR certolizumab pegol OR cimzia OR adalimumab OR humira OR golimumab OR simponi OR anti-tumor necrosis factor OR cyclosporine) AND

TS=(bacterial infection* OR mycoses OR fungal infection* OR viral disease* OR viral infection* OR tuberculosis OR histoplasmosis OR coccidioidmycosis)

MEDLINE (results returned=963)

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Supplemental Table 2: Estimated odds of serious infection for treatment strategies compared to aminosalicylates or antibiotics

Treatment Strategy	Comparator	Odds Ratio	Standard Error	95% Confidence Interval	
Antibiotic	Aminosalicylate	0.74	1.77	0.02	23.62
Tacrolimus	Aminosalicylate	0.86	2.46	0.01	107.46
Methotrexate+prednisone	Aminosalicylate	2.14	1.82	0.06	75.19
Azathioprine/6MP+prednisone	Aminosalicylate	1.73	2.08	0.03	101.16
Aminosalicylate+prednisone	Aminosalicylate	5.34	2.65	0.03	964.69
Budesonide+prednisone	Aminosalicylate	1.38	2.44	0.01	164.60
MMF+prednisone	Aminosalicylate	3.02	2.35	0.03	299.54
Infliximab+azathioprine/6MP	Aminosalicylate	0.80	1.38	0.05	12.00
Azathioprine/6MP+aminosalicylate	Aminosalicylate	0.98	2.44	0.01	117.79
Natalizumab+inflximab	Aminosalicylate	0.52	2.44	0.00	62.38
Infliximab+azathioprine/6MP+prednisone	Aminosalicylate	0.23	2.57	0.00	35.77
Tacrolimus	Antibiotic	1.17	2.29	0.01	103.85
Methotrexate+prednisone	Antibiotic	2.90	1.80	0.08	99.30
Azathioprine/6MP+prednisone	Antibiotic	2.34	2.06	0.04	133.97
Aminosalicylate+prednisone	Antibiotic	7.22	2.64	0.04	1283.38
Budesonide+prednisone	Antibiotic	1.86	2.43	0.02	218.73
MMF+prednisone	Antibiotic	4.08	2.34	0.04	397.65
Infliximab+azathioprine/6MP	Antibiotic	1.09	1.26	0.09	12.78
Azathioprine/6MP+aminosalicylate	Antibiotic	1.33	2.36	0.01	136.82
Natalizumab+infliximab	Antibiotic	0.70	2.33	0.01	67.10
Infliximab+azathioprine/6MP+prednisone	Antibiotic	0.31	2.57	0.00	47.57

Abbreviations: 6MP=6-mercaptopurine; MMF=mycophenolate mofetil

Supplemental Table 3: Estimated odds of serious infection for treatment strategies compared to anti-tumor necrosis factor biologics**

Treatment Strategy	Comparator	Odds Ratio	Standard Error	95% Confidence Interval	
Methotrexate	Infliximab	0.38	1.35	0.03	5.40
Azathioprine/6MP	Infliximab	1.05	0.47	0.42	2.63
Prednisone	Infliximab	1.41	0.75	0.32	6.13
Budesonide	Infliximab	1.46	1.60	0.06	33.90
Aminosalicylate	Infliximab	1.01	1.38	0.07	15.13
Antibiotic	Infliximab	0.75	1.16	0.08	7.29
Tacrolimus	Infliximab	0.87	2.07	0.02	50.35
Methotrexate+prednisone	Infliximab	2.16	1.39	0.14	32.92
Azathioprine/6MP+prednisone	Infliximab	1.74	1.72	0.06	50.37
Aminosalicylate+prednisone	Infliximab	5.38	2.38	0.05	571.50
Budesonide+prednisone	Infliximab	1.39	2.14	0.02	92.61
MMF+prednisone	Infliximab	3.04	2.03	0.06	163.96
Azathioprine/6MP+aminosalicylate	Infliximab	0.99	2.07	0.02	57.08
Natalizumab+infliximab	Infliximab	0.52	2.01	0.01	27.12
Methotrexate	Adalimumab	0.67	1.33	0.05	9.07
Azathioprine/6MP	Adalimumab	1.85	0.71	0.46	7.47
Prednisone	Adalimumab	2.49	0.93	0.41	15.27
Budesonide	Adalimumab	2.58	1.69	0.09	71.30
Aminosalicylate	Adalimumab	1.78	1.45	0.10	30.42
Antibiotic	Adalimumab	1.32	1.13	0.14	12.13
Tacrolimus	Adalimumab	1.54	2.05	0.03	86.01
Methotrexate+prednisone	Adalimumab	3.81	1.49	0.20	71.00
Azathioprine/6MP+prednisone	Adalimumab	3.08	1.80	0.09	104.79
Aminosalicylate+prednisone	Adalimumab	9.50	2.44	0.08	1137.24
Budesonide+prednisone	Adalimumab	2.45	2.21	0.03	186.68
MMF+prednisone	Adalimumab	5.37	2.11	0.09	332.76
Infliximab+azathioprine/6MP	Adalimumab	1.43	0.75	0.33	6.17
Azathioprine/6MP+aminosalicylate	Adalimumab	1.75	2.14	0.03	115.17
Natalizumab+infliximab	Adalimumab	0.93	2.09	0.02	56.03

Supplemental Table 3, cont.: Estimated odds of serious infection for treatment strategies compared to anti-tumor necrosis factor biologics**

Treatment Strategy	Comparator	Odds Ratio	Standard Error	95% Confidence Interval	
Infliximab+azathioprine/6MP+prednisone	Adalimumab	0.41	2.36	0.00	41.61
Methotrexate	Certolizumab pegol	0.22	1.37	0.01	3.23
Azathioprine/6MP	Certolizumab pegol	0.60	0.80	0.13	2.86
Prednisone	Certolizumab pegol	0.81	0.99	0.12	5.64
Budesonide	Certolizumab pegol	0.84	1.73	0.03	24.90
Aminosalicylate	Certolizumab pegol	0.58	1.49	0.03	10.75
Antibiotic	Certolizumab pegol	0.43	1.19	0.04	4.38
Tacrolimus	Certolizumab pegol	0.50	2.08	0.01	29.67
Methotrexate+prednisone	Certolizumab pegol	1.24	1.53	0.06	25.03
Azathioprine/6MP+prednisone	Certolizumab pegol	1.00	1.83	0.03	36.44
Aminiosalicylate+prednisone	Certolizumab pegol	3.09	2.47	0.02	388.64
Budesonide+prednisone	Certolizumab pegol	0.80	2.24	0.01	64.13
MMF+prednisone	Certolizumab pegol	1.75	2.13	0.03	114.62
Infliximab+azathioprine/6MP	Certolizumab pegol	0.46	0.83	0.09	2.34
Azathioprine/6MP+aminosalicylate	Certolizumab pegol	0.57	2.17	0.01	39.64
Natalizumab+infliximab	Certolizumab pegol	0.30	2.12	0.00	19.30
Infliximab+azathioprine/6MP+prednisone	Certolizumab pegol	0.13	2.38	0.00	14.25
Methotrexate	Golimumab	0.30	1.44	0.02	5.10
Azathioprine/6MP	Golimumab	0.83	0.91	0.14	4.92
Prednisone	Golimumab	1.12	1.08	0.13	9.35
Budesonide	Golimumab	1.16	1.78	0.04	38.35
Aminosalicylate	Golimumab	0.80	1.55	0.04	16.83
Antibiotic	Golimumab	0.59	1.26	0.05	7.06
Tacrolimus	Golimumab	0.69	2.13	0.01	44.90
Methotrexate+prednisone	Golimumab	1.72	1.59	0.08	39.05
Azathioprine/6MP+prednisone	Golimumab	1.39	1.88	0.03	55.79
Aminiosalicylate+prednisone	Golimumab	4.28	2.50	0.03	580.27

Supplemental Table 3, cont.: Estimated odds of serious infection for treatment strategies compared to anti-tumor necrosis factor biologics**

Treatment Strategy	Comparator	Odds Ratio	Standard Error	95% Confidence Interval	
Budesonide+prednisone	Golimumab	1.10	2.28	0.01	96.46
MMF+prednisone	Golimumab	2.42	2.18	0.03	173.09
Infliximab+azathioprine/6MP	Golimumab	0.64	0.93	0.10	4.01
Azathioprine/6MP+aminosalicylate	Golimumab	0.79	2.21	0.01	59.79
Natalizumab+infliximab	Golimumab	0.42	2.17	0.01	29.17
Infliximab+azathioprine/6MP+prednisone	Golimumab	0.18	2.42	0.00	21.32

Abbreviations: 6MP=6-mercaptopurine;
MMF=mycophenolate mofetil

**Other group comparisons can be found in Table 3

Supplemental Table 4: Estimated odds of serious infection for treatment strategies compared to immunomodulators**

Treatment Strategy	Comparator	Odds Ratio	Standard Error	95% Confidence Interval	
Prednisone	Methotrexate	3.69	1.53	0.18	74.75
Budesonide	Methotrexate	3.83	2.09	0.06	229.95
Aminosalicylate	Methotrexate	2.64	1.90	0.06	108.59
Antibiotic	Methotrexate	1.95	1.67	0.07	51.32
Tacrolimus	Methotrexate	2.28	2.39	0.02	247.08
Methotrexate+prednisone	Methotrexate	5.65	1.93	0.13	248.43
Azathioprine/6MP+prednisone	Methotrexate	4.57	2.18	0.06	325.34
Aminosalicylate+prednisone	Methotrexate	14.09	2.73	0.07	2976.15
Budesonide+prednisone	Methotrexate	3.63	2.53	0.03	514.62
MMF+prednisone	Methotrexate	7.97	2.44	0.07	942.50
Infliximab+azathioprine/6MP	Methotrexate	2.12	1.43	0.13	35.20
Azathioprine/6MP+aminosalicylate	Methotrexate	2.60	2.46	0.02	323.57
Natalizumab+infliximab	Methotrexate	1.37	2.43	0.01	159.17
Infliximab+azathioprine/6MP+prednisone	Methotrexate	0.61	2.66	0.00	110.87
Budesonide	Azathioprine/6MP	1.40	1.61	0.06	32.63
Aminosalicylate	Azathioprine/6MP	0.96	1.38	0.06	14.37
Antibiotic	Azathioprine/6MP	0.71	1.24	0.06	8.04
Tacrolimus	Azathioprine/6MP	0.83	2.11	0.01	52.20
Methotrexate+prednisone	Azathioprine/6MP	2.06	1.40	0.13	31.74
Azathioprine/6MP+prednisone	Azathioprine/6MP	1.66	1.72	0.06	48.46
Aminosalicylate+prednisone	Azathioprine/6MP	5.13	2.38	0.05	548.49
Budesonide+prednisone	Azathioprine/6MP	1.32	2.15	0.02	88.93
MMF+prednisone	Azathioprine/6MP	2.90	2.04	0.05	157.53
Azathioprine/6MP+aminosalicylate	Azathioprine/6MP	0.95	2.01	0.02	48.96
Natalizumab+infliximab	Azathioprine/6MP	0.50	2.07	0.01	28.76
Infliximab+azathioprine/6MP+prednisone	Azathioprine/6MP	0.22	2.30	0.00	19.99

Abbreviations: 6MP=6-mercaptopurine; MMF=mycophenolate mofetil

**Other group comparisons can be found in Table 4

Supplemental Table 5: Estimated odds of serious infection for treatment strategies compared to other immunosuppressants

Treatment Strategy	Comparator	Odds Ratio	Standard Error	95% Confidence Interval	
Budesonide	Prednisone	1.04	1.42	0.06	16.70
Aminosalicylate	Prednisone	0.71	1.39	0.05	10.84
Antibiotic	Prednisone	0.53	1.37	0.04	7.77
Tacrolimus	Prednisone	0.62	2.19	0.01	45.52
Methotrexate+prednisone	Prednisone	1.53	1.17	0.15	15.19
Azathioprine/6MP+prednisone	Prednisone	1.24	1.54	0.06	25.50
Aminosalicylate+prednisone	Prednisone	3.82	2.26	0.05	319.84
Budesonide+prednisone	Prednisone	0.98	2.01	0.02	50.38
MMF+prednisone	Prednisone	2.16	1.89	0.05	87.89
Infliximab+Azathioprine/6MP	Prednisone	0.57	0.61	0.17	1.90
Azathioprine/6MP+aminosalicylate	Prednisone	0.70	2.15	0.01	47.78
Natalizumab+infliximab	Prednisone	0.37	2.15	0.01	25.07
Infliximab+Azathioprine/6MP+prednisone	Prednisone	0.16	2.17	0.00	11.54
Aminosalicylate	Budesonide	0.69	1.98	0.01	33.60
Antibiotic	Budesonide	0.51	1.97	0.01	24.31
Tacrolimus	Budesonide	0.60	2.61	0.00	99.52
Methotrexate+prednisone	Budesonide	1.47	1.84	0.04	54.17
Azathioprine/6MP+prednisone	Budesonide	1.19	2.10	0.02	72.48
Aminosalicylate+prednisone	Budesonide	3.68	2.67	0.02	685.33
Budesonide+prednisone	Budesonide	0.95	2.46	0.01	117.21
MMF+prednisone	Budesonide	2.08	2.36	0.02	213.66
Infliximab+Azathioprine/6MP	Budesonide	0.55	1.54	0.03	11.38
Azathioprine/6MP+aminosalicylate	Budesonide	0.68	2.58	0.00	105.84
Natalizumab+infliximab	Budesonide	0.36	2.57	0.00	55.60
Infliximab+Azathioprine/6MP+prednisone	Budesonide	0.16	2.59	0.00	25.44

Abbreviations: 6MP=6-mercaptopurine; MMF=mycophenolate mofetil

Supplemental Table 5, cont.: Estimated odds of serious infection for treatment strategies compared to other immunosuppressants

Treatment Strategy	Comparator	Odds Ratio	Standard Error	95% Confidence Interval	
Methotrexate+prednisone	Tacrolimus	2.48	2.49	0.02	324.07
Azathioprine/6MP+prednisone	Tacrolimus	2.00	2.68	0.01	384.33
Aminosalicylate+prednisone	Tacrolimus	6.18	3.15	0.01	2959.71
Budesonide+prednisone	Tacrolimus	1.59	2.97	0.00	541.43
MMF+prednisone	Tacrolimus	3.49	2.90	0.01	1019.73
Infliximab+Azathioprine/6MP	Tacrolimus	0.93	2.12	0.01	59.75
Azathioprine/6MP+aminosalicylate	Tacrolimus	1.14	2.92	0.00	347.20
Natalizumab+infliximab	Tacrolimus	0.60	2.89	0.00	172.75
Infliximab+Azathioprine/6MP+prednisone	Tacrolimus	0.27	3.08	0.00	112.45

Abbreviations: 6MP=6-mercaptopurine; MMF=mycophenolate mofetil

Supplemental Table 6: Estimated odds of serious infection for treatment strategies compared to other biologics**

Treatment Strategy	Comparator	Odds Ratio	Standard Error	95% Confidence Interval	
Methotrexate	Natalizumab	0.65	1.34	0.05	8.97
Azathioprine/6MP	Natalizumab	1.79	0.73	0.43	7.52
Prednisone	Natalizumab	2.41	0.94	0.38	15.23
Budesonide	Natalizumab	2.50	1.70	0.09	70.20
Aminosalicylate	Natalizumab	1.72	1.46	0.10	30.04
Antibiotic	Natalizumab	1.27	1.15	0.14	12.03
Tacrolimus	Natalizumab	1.49	2.06	0.03	84.45
Methotrexate+prednisone	Natalizumab	3.69	1.50	0.19	70.06
Azathioprine/6MP+prednisone	Natalizumab	2.98	1.81	0.09	103.08
Aminosalicylate+prednisone	Natalizumab	9.20	2.45	0.08	1114.31
Budesonide+prednisone	Natalizumab	2.37	2.22	0.03	183.13
MMF+prednisone	Natalizumab	5.21	2.11	0.08	326.63
Infliximab+azathioprine/6MP	Natalizumab	1.38	0.76	0.31	6.19
Azathioprine/6MP+aminosalicylate	Natalizumab	1.70	2.14	0.03	113.03
Natalizumab+infliximab	Natalizumab	0.90	2.10	0.01	55.00
Infliximab+azathioprine/6MP+prednisone	Natalizumab	0.40	2.36	0.00	40.79
Methotrexate	Ustekinumab	1.29	1.37	0.09	18.72
Azathioprine/6MP	Ustekinumab	3.54	0.78	0.76	16.41
Prednisone	Ustekinumab	4.76	0.98	0.70	32.54
Budesonide	Ustekinumab	4.94	1.72	0.17	144.78
Aminosalicylate	Ustekinumab	3.40	1.48	0.19	62.40
Antibiotic	Ustekinumab	2.51	1.18	0.25	25.35
Tacrolimus	Ustekinumab	2.94	2.08	0.05	172.81
Methotrexate+prednisone	Ustekinumab	7.28	1.53	0.36	145.33
Azathioprine/6MP+prednisone	Ustekinumab	5.88	1.83	0.16	212.01
Aminosalicylate+prednisone	Ustekinumab	18.15	2.46	0.15	2266.86

Supplemental Table 6, cont.: Estimated odds of serious infection for treatment strategies compared to other biologics**

Treatment Strategy	Comparator	Odds Ratio	Standard Error	95% Confidence Interval	
Budesonide+prednisone	Ustekinumab	4.68	2.24	0.06	373.75
MMF+prednisone	Ustekinumab	10.26	2.13	0.16	667.76
Infliximab+azathioprine/6MP	Ustekinumab	2.73	0.81	0.55	13.46
Azathioprine/6MP+aminosalicylate	Ustekinumab	3.34	2.16	0.05	230.95
Natalizumab+infliximab	Ustekinumab	1.77	2.12	0.03	112.46
Infliximab+azathioprine/6MP+prednisone	Ustekinumab	0.78	2.38	0.01	83.07
Methotrexate	Vedolizumab	0.69	1.33	0.05	9.36
Azathioprine/6MP	Vedolizumab	1.89	0.72	0.46	7.77
Prednisone	Vedolizumab	2.55	0.93	0.41	15.82
Budesonide	Vedolizumab	2.64	1.70	0.10	73.46
Aminosalicylate	Vedolizumab	1.82	1.45	0.11	31.38
Antibiotic	Vedolizumab	1.35	1.14	0.14	12.54
Tacrolimus	Vedolizumab	1.57	2.06	0.03	88.50
Methotrexate+prednisone	Vedolizumab	3.90	1.50	0.21	73.22
Azathioprine/6MP+prednisone	Vedolizumab	3.15	1.80	0.09	107.91
Aminosalicylate+prednisone	Vedolizumab	9.72	2.44	0.08	1169.11
Budesonide+prednisone	Vedolizumab	2.50	2.21	0.03	192.01
MMF+prednisone	Vedolizumab	5.50	2.11	0.09	342.35
Infliximab+azathioprine/6MP	Vedolizumab	1.46	0.75	0.33	6.41
Azathioprine/6MP+aminosalicylate	Vedolizumab	1.79	2.14	0.03	118.48
Natalizumab+infliximab	Vedolizumab	0.95	2.10	0.02	57.64
Infliximab+azathioprine/6MP+prednisone	Vedolizumab	0.42	2.36	0.00	42.79

Abbreviations: 6MP=6-mercaptopurine; MMF=mycophenolate mofetil

**Other group comparisons can be found in Table 4

Supplemental Table 7: Estimated odds of serious infection for treatment strategies compared to combination therapies

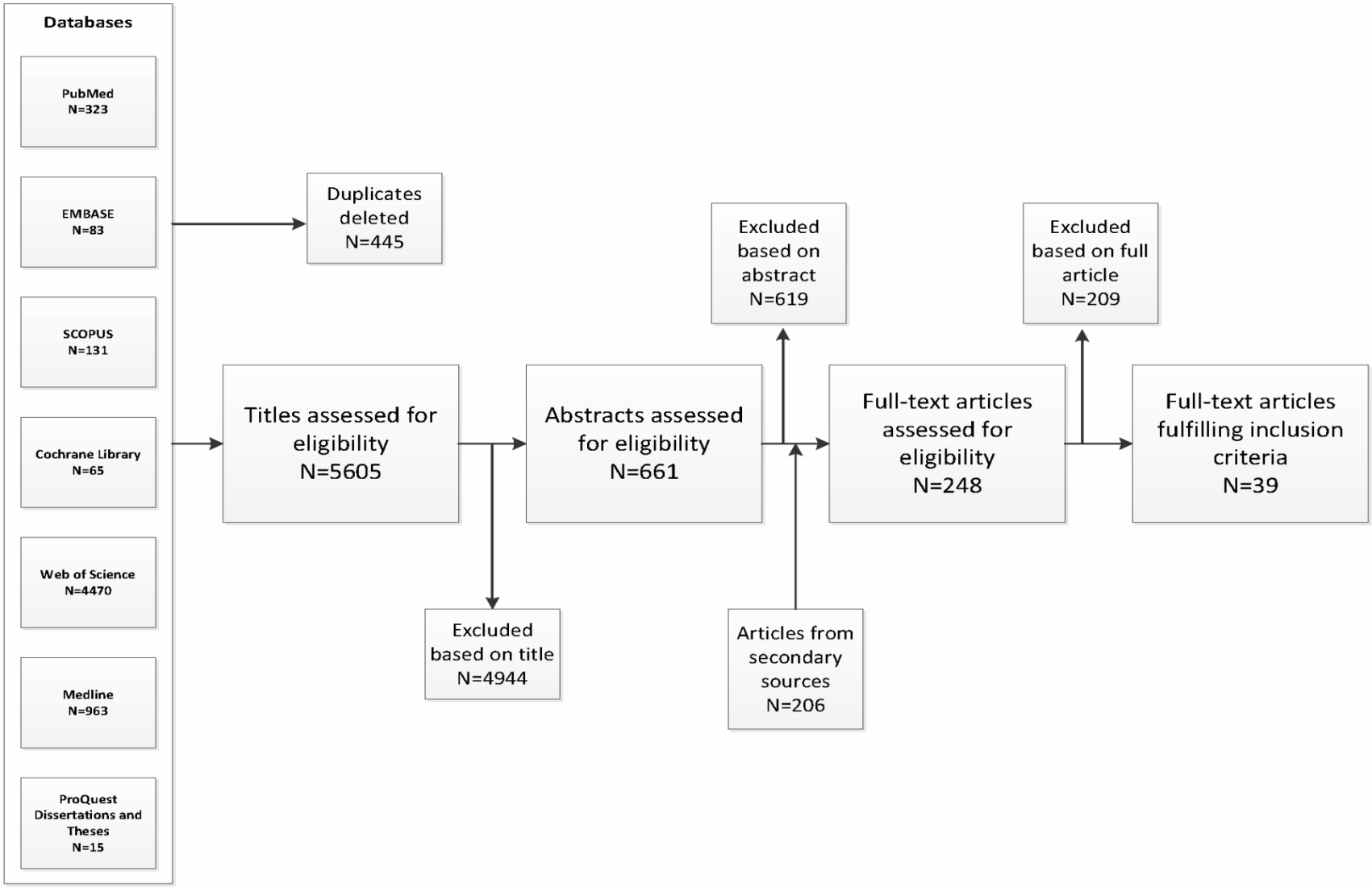
Treatment Strategy	Comparator	Odds Ratio	Standard Error	95% Confidence Interval	
Azathioprine/6MP+prednisone	Methotrexate+prednisone	0.81	1.54	0.04	16.64
Aminosalicylate+prednisone	Methotrexate+prednisone	2.49	2.26	0.03	208.77
Budesonide+prednisone	Methotrexate+prednisone	0.64	2.32	0.01	61.21
MMF+prednisone	Methotrexate+prednisone	1.41	1.89	0.03	57.36
Infliximab+azathioprine/6MP	Methotrexate+prednisone	0.38	1.32	0.03	4.99
Azathioprine/6MP+aminosalicylate	Methotrexate+prednisone	0.46	2.45	0.00	55.97
Natalizumab+infliximab	Methotrexate+prednisone	0.24	2.45	0.00	29.39
Infliximab+azathioprine/6MP+prednisone	Methotrexate+prednisone	0.11	2.17	0.00	7.54
Aminosalicylate+prednisone	Azathioprine/6MP+prednisone	3.08	1.65	0.12	78.27
Budesonide+prednisone	Azathioprine/6MP+prednisone	0.79	2.53	0.01	113.94
MMF+prednisone	Azathioprine/6MP+prednisone	1.74	1.09	0.21	14.84
Infliximab+azathioprine/6MP	Azathioprine/6MP+prednisone	0.46	1.66	0.02	12.00
Azathioprine/6MP+aminosalicylate	Azathioprine/6MP+prednisone	0.57	2.65	0.00	102.17
Natalizumab+infliximab	Azathioprine/6MP+prednisone	0.30	2.65	0.00	53.68
Infliximab+azathioprine/6MP+prednisone	Azathioprine/6MP+prednisone	0.13	1.52	0.01	2.63
Budesonide+prednisone	Aminosalicylate+prednisone	0.26	3.02	0.00	96.49
MMF+prednisone	Aminosalicylate+prednisone	0.57	1.98	0.01	27.34
Infliximab+azathioprine/6MP	Aminosalicylate+prednisone	0.15	2.34	0.00	14.77
Azathioprine/6MP+aminosalicylate	Aminosalicylate+prednisone	0.18	3.12	0.00	83.51
Natalizumab+infliximab	Aminosalicylate+prednisone	0.10	3.12	0.00	43.91
Infliximab+azathioprine/6MP+prednisone	Aminosalicylate+prednisone	0.04	2.25	0.00	3.52
MMF+prednisone	Budesonide+prednisone	2.19	2.76	0.01	489.43
Infliximab+azathioprine/6MP	Budesonide+prednisone	0.58	2.10	0.01	35.71
Azathioprine/6MP+aminosalicylate	Budesonide+prednisone	0.71	2.94	0.00	229.24
Natalizumab+infliximab	Budesonide+prednisone	0.38	2.94	0.00	120.52
Infliximab+azathioprine/6MP+prednisone	Budesonide+prednisone	0.17	2.96	0.00	54.91

Supplemental Table 7, cont.: Estimated odds of serious infection for treatment strategies compared to combination therapies

Treatment Strategy	Comparator	Odds Ratio	Standard Error	95% Confidence Interval	
Infliximab+azathioprine/6MP	MMF+prednisone	0.27	1.99	0.01	13.07
Azathioprine/6MP+aminosalicylate	MMF+prednisone	0.33	2.87	0.00	89.51
Natalizumab+infliximab	MMF+prednisone	0.17	2.86	0.00	47.05
Infliximab+azathioprine/6MP+prednisone	MMF+prednisone	0.08	1.87	0.00	3.00
Azathioprine/6MP+aminosalicylate	Infliximab+azathioprine/6MP	1.22	2.08	0.02	71.56
Natalizumab+infliximab	Infliximab+azathioprine/6MP	0.65	2.08	0.01	37.86
Infliximab+azathioprine/6MP+prednisone	Infliximab+azathioprine/6MP	0.29	2.25	0.00	23.70
Natalizumab+infliximab	Azathioprine/6MP+aminosalicylate	0.53	2.89	0.00	151.42
Infliximab+azathioprine/6MP+prednisone	Azathioprine/6MP+aminosalicylate	0.23	3.06	0.00	93.36
Infliximab+azathioprine/6MP+prednisone	Natalizumab+infliximab	0.44	3.05	0.00	175.71

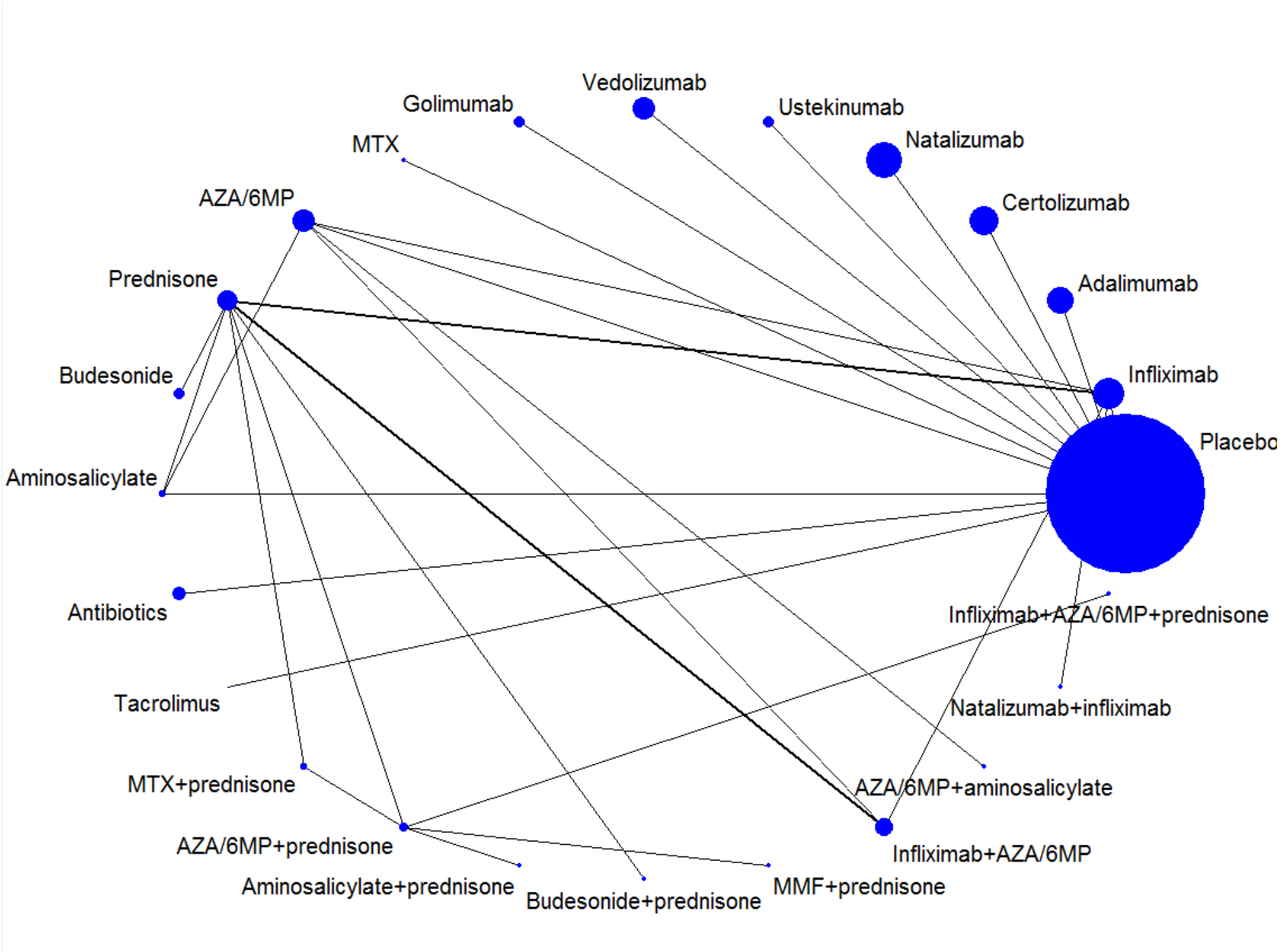
Abbreviations: 6MP=6-mercaptopurine; MMF=mycophenolate mofetil

Figure 1: PRISMA* Flowchart depicting the identification of studies, inclusion, and exclusion assessment



*PRISMA-Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Figure 2: Network of clinical trials of pharmacological treatment strategies for adults with inflammatory bowel disease (IBD).



Each node in the network represents a treatment strategy and the connections signify pairwise treatment comparisons from the trials included.

CHAPTER 3: WORLDWIDE INCIDENCE OF COLORECTAL CANCER, LEUKEMIA, AND LYMPHOMA IN INFLAMMATORY BOWEL DISEASE (IBD): AN UPDATED SYSTEMATIC REVIEW AND META-ANALYSIS

Abstract

Introduction: Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is associated with an increased risk of colorectal cancer (CRC). In addition, there are concerns regarding the association between lymphoproliferative disorders such as leukemia and lymphoma and IBD. We conducted a systematic review and meta-analysis of the existing IBD literature to estimate the incidence of CRC, leukemia, and lymphoma in adult IBD patients.

Methods: Studies were identified by a literature search of PubMed, Cochrane Library, Medline, Web of Science, Scopus, EMBASE, and ProQuest Dissertations and Theses. Pooled incidence rates (per 100,000 person-years [py]) were calculated through use of a random effects model, unless substantial heterogeneity prevented pooling of estimates. Several stratified analyses and meta-regression were performed to explore potential study heterogeneity and bias.

Results: Thirty-six articles fulfilled the inclusion criteria. For CRC, the pooled incidence rate in CD was 53.3/100,000 py (95% CI 46.3 – 60.3/100,000). The incidence of leukemia was 1.5/100,000 py (95% CI -0.06 – 3.0/100,000) in IBD, 0.3/100,000 py (95% CI -1.0 – 1.6/100,000) in CD and 13.0/100,000 py (95% CI 5.8 – 20.3/100,000) in UC. For lymphoma, the pooled incidence rate in CD was 0.8/100,000 py (95% CI -0.4 – 2.1/100,000). Substantial heterogeneity prevented the pooling of other incidence estimates.

Discussion: The incidence of CRC, leukemia, and lymphoma in IBD is low. These findings provide a better understanding of the underlying risk of these cancers in the IBD population.

Introduction

Colorectal cancer (CRC) incidence is higher in inflammatory bowel disease (IBD) patients than in the general population, and CRC accounts for an estimated 10-15% of deaths in patients with IBD.[1] The risk conferred by IBD may be due to chronic inflammation combined with genetic factors.[1-3] Patients with extensive inflammation, a younger age at diagnosis, long disease duration, comorbid primary sclerosing cholangitis (PSC), and pseudopolyposis are at the highest risk.[4-14]

IBD patients receiving immunomodulators may also be at higher risk of lymphoproliferative disorders such as lymphoma and leukemia.[15-17] The risk of lymphoma in IBD patients is low, but appears to be higher than in the general population.[6,8,14,18] The risk of leukemia in IBD is less clear.[6,8,14,19]

Understanding the risk for development of these malignancies inherent to IBD is crucial for cancer surveillance strategies. In addition, determination of the absolute increase in risk of these malignancies from IBD pharmacotherapy is a crucial consideration for providers and patients. The aims of this study are to estimate the incidence of CRC, leukemia, and lymphoma in adult IBD patients through a systematic review and meta-analysis. Unique to this study, we attempt to evaluate the underlying risk of these cancers in IBD overall, and separately Crohn's disease (CD) and ulcerative colitis (UC), and excluding the effects of IBD pharmacotherapy (specifically

immunomodulators and biologics), given evidence these medications may increase cancer risk.

Methods

Literature Search

A detailed literature search was conducted to identify all published and unpublished studies examining the incidence of CRC, leukemia, and lymphoma in adult IBD patients. We searched the PubMed, Cochrane Library, Medline, Web of Science, Scopus, EMBASE, and ProQuest Dissertations and Theses databases. Reference lists of published articles were hand searched for secondary sources, and experts in the field contacted for unpublished data. Furthermore, ClinicalTrials.gov, the WHO International Clinical Trial Registry, and scientific information packets of approved IBD pharmacotherapies were scrutinized for additional information sources. No restrictions on language, country of origin, or publication date were used. Figure 1 outlines the literature search and Supplementary Table 1 details the search strategy employed.

Inclusion and Exclusion Criteria

All studies that reported incidence or provided information sufficient to accurately calculate incidence for the three cancers of interest in adult IBD patients were included. Studies focusing on pediatric populations, not reporting person-years of follow up, of duration less than one year, and not written in English and unable to be translated to English were excluded. If publications reported duplicate data on a population, only the publication with the longest follow-up period was included.

Data Collection and Quality Assessment

Two independent reviewers (CW and KCS) examined each article for inclusion according to the eligibility criteria. Any disagreement was resolved through discussion and consensus. Thirty-six articles fulfilled the inclusion criteria.[7,8,10,11,13,14,19-48] Figure 1 outlines the search flowchart.

We retrieved demographic (where possible) and outcome data for each included article using standardized forms. Individual studies were assigned a bias risk rating using the Cochrane Collaboration's Risk of Bias Assessment Tool: for Non-Randomized Studies of Interventions (ACROBAT-NRSI).[49] The strength of evidence for each cancer was assessed utilizing The Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach.[50]

Statistical Analysis

Individual study unadjusted incidence rates (per 100,000 person-years [py]) were calculated from the reported number of cancer cases and person-years of follow up for each outcome separately. Standard errors and 95% confidence intervals (CI) were estimated assuming a Poisson distribution.[51] In situations with zero observed cases, the value of 3.7 was used to calculate incidence rates and the confidence interval upper limit.[51]

As our interest is in quantifying the incidence rate of CRC, leukemia, and lymphoma in IBD patients not treated with immunomodulators or biologic agents (and treatment information is often unreported), two stratification variables were created using study publication year as an estimate of when each medication class became widely used. 1995 was used as the dividing year for widespread immunomodulator use

and 2000 for biologic use. Pooled incidence rates with 95% CIs were then calculated for 1) each cancer overall, 2) each cancer in CD and UC separately, 3) each cancer stratified by year of publication, and 4) each cancer stratified by country of origin (to determine if incidence varied by geographic region). A random effects model was used to account for potential between study variations. The I^2 statistic was used to quantify the percentage of heterogeneity for all pooled estimates from between study variation, with ≥75% indicating substantial heterogeneity.[52] Publication bias and the presence of other small study effects were measured through visual assessment of funnel plot symmetry and Egger's test.[52] Sensitivity analyses were undertaken to explore potential sources of heterogeneity. Meta-regression was used to further test the effects of study- and subject- level covariates on cancer risk, as well as the degree of between study heterogeneity explained by the covariates through calculation of the adjusted R^2. The adjusted R^2 measures the relative reduction in the between study variance explained by the covariates in the model, and is presented as a percentage.[52] Statistical analysis was performed using Stata (StataCorp, College Station, TX). P-values of ≤ .05 were considered statistically significant.

Results

Colorectal Cancer

Reported incidence rates of CRC in IBD ranged from 41.5/100,000 py (95% CI 24.5 – 58.5/100,000) to 543.5/100,000 py (95% CI 316.4 – 770.6/100,000) [Table 1]. Substantial heterogeneity prevented pooling of estimates using a random effects model (heterogeneity test, chi^2=173.63; p<0.001; I^2=86.2%). Therefore, we present unpooled incidence estimates. Separate sensitivity analyses excluding the studies with

the highest individual incidence estimate[34] and the study with the greatest weight on the pooled estimate[7] did not significantly change the degree of heterogeneity present.

Reported CRC incidence rates in CD ranged from 19.5/100,000 py (95% CI 0.4 – 38.6/100,000) to 344.9/100,000 py (95% CI 105.9 – 583.9/100,000). [Table 1] Using a random effects model, an estimated incidence of CRC in CD of 53.3/100,000 py (95% CI 46.3 – 60.3/100,000) was obtained. Figure 2 displays the Forest plot for the pooled estimates. In UC, the reported incidence rates ranged from 54.5/100,000 py (95% CI 30.0 – 79.0/100,000) to 543.5/100,000 py (95% CI 316.4 – 770.6/100,000). Substantial heterogeneity was again present when pooling using a random effects model (heterogeneity test, chi^2=110.67; p<0.001; I^2=86.4%), and thus the results in UC were not pooled.

Analyses stratified by publication year and region of origin did not reveal any significant differences in results. We also conducted meta-regression analyses to evaluate the potential impact of age, gender, race, Montreal Classification, disease duration, surgical history, smoking status, comorbid primary sclerosing cholangitis, presence of extraintestinal manifestations, and concomitant treatment with immunosuppressants and/or biologics on the CRC incidence in IBD. Due to the limited sample size and incomplete reporting of demographic characteristics in many studies, these analyses were underpowered. Together, age, gender, and disease duration explained a significant proportion of the between study variability (adjusted R^2=65.67%); however we could not make any further conclusions regarding the impact of these covariates on CRC incidence in IBD. Evaluation of funnel plots and Egger's test showed evidence of small study effects and/or publication bias for IBD overall

(p=0.121), and weak evidence of small study effects in CD and UC (p=0.004 CD; p=0.05 UC). However, the power of these tests may be compromised due to small sample sizes and significant heterogeneity between studies. Given the observational nature of the included studies and the probability of bias from small study effects, the overall quality of the CRC body of evidence per the GRADE approach is low.

Leukemia

Reported incidence rates of leukemia in IBD ranged from 0.0/100,000 py (95% CI 0.0 – 3.7/100,000) to 28.4/100,000 py (95% CI -3.7 – 60.5/100,000) [Table 2]. Using a random effects model, the pooled estimated incidence of leukemia in IBD of 1.5/100,000 py was obtained (95% CI -0.06 – 3.0/100,000). Figure 3 illustrates the Forest plot for the pooled estimates. Moderate between study heterogeneity was seen (heterogeneity test chi^2=22.96, p=0.003; I^2 65.2%); however this is likely influenced by the small number of available studies. In CD, the range of reported incidence rates was identical to that of IBD. [Table 2] In UC, reported incidence rates ranged from 8.97/100,000 py (95% CI 0.2 – 17.8/100,000) to 25.4/100,000 py (95% CI -9.8 – 60.6/100,000). [Table 2] The pooled incidence estimate was 0.3/100,000 py for CD (95% CI -1.0 – 1.6/100,000) and 13.0/100,000 py for UC (95% CI 5.8 – 20.3/100,000). The I^2 statistics are 49.0% (heterogeneity test, chi^2=9.81, p=0.081) and 0.0% (heterogeneity test, chi^2=2.65, p=0.449) respectively, indicating low levels of heterogeneity; however the power of this analysis is severely limited due to the small number of included studies.

Stratification by publication year and region did not impact the incidence estimates for IBD or for CD and UC separately. Furthermore, no significant effects of

any study- or subject- level covariates on incidence estimates were discovered in meta-regression analyses; however the small sample size again restricted the power of these tests.

As less than 10 studies were included, the interpretation of funnel plot symmetry and Egger's test to assess for the presence of small study effects and/or publication bias are not recommended.[52] The overall quality of the leukemia body of evidence, per the GRADE approach, is low due to study designs and small sample size.

Lymphoma

Reported incidence rates for lymphoma in IBD ranged from 0.0/100,000 py (95% CI 0.0 – 3.7/100,000) to 81.7/100,000 py (95% CI 21.2 – 142.2/100,000). [Table 3] Substantial heterogeneity between studies prevented pooling of estimates (heterogeneity test, chi^2=568.12; p<0.001; I^2=96.7%). Thus, the included studies are presented as unpooled estimates. A sensitivity analysis excluding the two studies with the lowest individual incidence estimates and highest weights on the pooled estimates was conducted, with no significant corresponding decrease in heterogeneity.[14,39]

Reported incidence rates of lymphoma in CD ranged from 0.0/100,000 py (95% CI 0.0 – 3.7/100,000) to 36.8/100,000 py (95% CI -35.3 – 108.9/100,000). [Table 3] For UC, the incidence rates ranged from 0.0/100,000 py (95% CI 0.0 – 3.7/100,000) to 76.2/100,000 py (95% CI 15.2 – 137.2/100,000). [Table 3] A pooled incidence rate of 0.8/100,000 py (95% CI -0.4 – 2.1/100,000) for CD was obtained. Substantial heterogeneity prevented pooling of estimates for UC (heterogeneity test, chi^2=199.52; p<0.001; I^2=94.5%). A sensitivity analysis excluding the study with the largest impact on the pooled estimate in UC [36] decreased the heterogeneity (heterogeneity test,

chi^2=44.79; p<0.001; I^2=77.7%). However, substantial heterogeneity remained, and results for UC are presented as unpooled estimates. [Figure 4]

Incidence estimates stratified by publication year and region did not differ. Meta-regression analysis revealed a statistically significant effect of age on lymphoma incidence in IBD. For each mean year increase in age, the incidence of lymphoma increased by approximately 2.1/100,000 py (95% CI 0.74 – 3.4/100,000), explaining approximately 65.8% of the between study heterogeneity (adjusted R^2=65.8%). No other covariate effects were found in meta-regression analyses.

There was weak evidence of publication bias and/or small study effects in the IBD analysis (p=0.213) and in the UC analysis (p=0.824). The number of included studies for CD is less than 10; thus analyses of funnel plots and Egger's test are not recommended.[52] The overall quality of the lymphoma body of evidence, per the GRADE approach, is low due to the observational designs of available studies.

Discussion

This meta-analysis was performed in order to produce updated and reliable incidence rates for CRC, leukemia, and lymphoma in IBD patients, and in CD and UC separately. We aimed to quantify cancer incidence associated with underlying IBD, without the effects of immunomodulator and biologic pharmacotherapy, but this was difficult without reliable reporting of treatment information in the available studies. Although we could not pool estimates of the incidence of CRC in IBD and UC specifically, a pooled incidence rate of 53.3/100,000 py (95% CI 46.3 – 60.3/100,000) in CD was obtained. The estimated worldwide CRC incidence rate is 19.3/100,000 py.[53] In more developed regions of the World, which compares to the regions of origin of the

included studies, the incidence rate is higher at 59.2/100,000 py,[53]. As such, CRC incidence in CD does not appear to be higher than that of the general population in similar areas of origin. Of note, these incidence estimates are crude (not age-adjusted), and therefore may not reflect differences in the age of the underlying populations.

For leukemia, pooled incidence rates of 1.5/100,000 py (95% CI -0.06 – 3.0/100,000), 0.3/100,000 py (95% CI -1.0 – 1.6/100,000) and 13.0/100,000 py (95% CI 5.8 – 20.3/100,000) were obtained for IBD, CD, and UC respectively. The estimated worldwide leukemia incidence is 5.0/100,000 py, and 11.3/100,00 py in developed regions.[53] Thus, the incidence of leukemia in IBD and CD is lower than that of the general population in developed regions, but is slightly higher in UC. For lymphoma, substantial heterogeneity prevented the pooling of estimates for IBD and UC; however a pooled incidence rate of 0.8/100,000 py (95% CI -0.4 – 2.1/100,000) in CD was obtained. Estimated worldwide lymphoma incidence is 6.4/100,000 py, and 17.6/100,000 py in more developed areas.[53] Thus, the incidence of lymphoma in CD is lower than estimated both world-wide and in developed regions.

Due to incomplete reporting of use of immunomodulators and biologics in the published literature, we could not calculate incidence rates of CRC, leukemia, and lymphoma specifically in persons not treated with these medications; however incidence estimates stratified by publication year before and after widespread use of these medications were not significantly different. This suggests that the impact of immunomodulators and biologics on the incidence of these cancers may be negligible. Meta-regression did not reveal any significant subject or study level covariate effects in the majority of analyses, with the exception of the effect of mean age on the incidence

of lymphoma in IBD. The power of these tests was limited by incomplete reporting of these variables and the small number of included studies.

The strength of the present study is the comprehensiveness of the literature search and evaluation of data for inclusion. Despite the exhaustiveness of the search, we could include only a small number of studies, limiting the power of the pooled analyses and ultimate confidence in incidence estimates. In addition, substantial heterogeneity prevented pooling of estimates in some cases. The heterogeneity of the included studies may reflect differences in follow-up time, cohort size, geographic differences in patient care, or other factors that we were unable to assess due to incomplete reporting in the published literature. Although these limitations may lead to bias in our incidence estimates, the direction of which is indeterminable, our estimates are based on the best available evidence.

In conclusion, this meta-analysis presents updated estimates of the incidence of CRC, leukemia, and lymphoma in adults with IBD. Overall, the incidence of these malignancies does not appear to be higher than in the general population, with the exception of a slightly elevated risk of leukemia in UC. These results may be used to better understand the underlying risk of these cancers in patients with IBD. Further research is needed to explore patient characteristics that may modify the risk for malignancy. Specifically, we need large population based cohort studies in IBD patients that report complete demographic and outcome data. Detailed information on immunomodulator and biologic use is limited in the published literature, and if we are to be able to truly understand the potential increased risk of malignancy associated with IBD pharmacotherapy, this information is required.

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Tables and Figures

Table 1: Characteristics of included studies of CRC in IBD

Author	Journal	Publication Year	Study Design	Region of Origin	Number of Sites	Study Duration (yrs)	Person Years	Number of Patients	Diagnosis	Mean Age (yrs)	Female (%)	Mean Disease Duration (yrs)	Surgery (%)	PSC (%)	Pancolitis (%)	Immunomodulator Use (%)	Biologic Use (%)	Observed Number of CRCs	Incidence Rate (per 100,000 persons)	Standard Error	95% CI Lower Bound	95% CI Upper Bound	Bias Rating
Askling[21]	Gastroenterology	2001	Cohort	Europe (Western)	Countrywide	54	169,332	19,459	IBD		48.6				10.3			143	84.4	7.1	70.6	98.2	Moderate
							91,833	*8,810*	*CD*		*53.0*				*17.0*			*40*	*43.6*	*6.9*	*30.1*	*57.1*	
							77,499	*10,649*	*UC*		*45.0*				*4.8*			*103*	*132.9*	*13.1*	*107.2*	*158.6*	
Bernstein[23]	Cancer	2001	Case-control	Canada	Regionwide	14	41,005	5,529	IBD	39.0	54.5					0.0	0.0	60	146.3	18.9	109.3	183.3	Moderate
							21,340	*2,857*	*CD*	*36.3*	*59.0*					*0.0*	*0.0*	*24*	*112.5*	*23.0*	*67.5*	*157.5*	
							19,665	*2,672*	*UC*	*41.7*	*50.0*					*0.0*	*0.0*	*36*	*183.1*	*30.5*	*123.3*	*242.9*	
Farrell[25]	Gut	2000	Cohort	Europe (Western)	1	9	6,256	782	IBD*	44.1	52.0	10.0			26.0	30.0		3	48.0	27.7	-6.3	102.3	Moderate
Fraser[26]	Aliment Pharmacol Ther	2002	Cohort	Europe (Western)	Countrywide	35	55,388	1,578	IBD	35.0	53.0				30.0	0.0	0.0	23	41.5	8.7	24.5	58.5	Moderate
							20,494	*584*	*CD*							*0.0*	*0.0*	*4*	*19.5*	*9.8*	*0.4*	*38.6*	
							34,894	*994*	*UC*							*0.0*	*0.0*	*19*	*54.5*	*12.5*	*30.0*	*79.0*	
Gillen[27]	Gut	1994	Cohort	Europe (Western)	Countrywide	30	12,324	611	IBD									37	300.2	49.4	203.5	396.9	Moderate
							2,320	*125*	*CD*									*8*	*344.9*	*121.9*	*105.9*	*583.9*	
							10,004	*486*	*UC*									*29*	*289.9*	*53.8*	*184.4*	*395.4*	
Herrinton[29]	Gastroenterology	2012	Cohort	United States	Countrywide	12	61,793	14,875	IBD	61.8								82	132.7	14.7	104.0	161.4	Moderate
							28,469	*5,053*	*CD*	*62.4*								*29*	*101.9*	*18.9*	*64.8*	*139.0*	
							33,324	*9,822*	*UC*	*61.1*								*53*	*159.0*	*21.8*	*116.2*	*201.8*	
Hou[30]	Inflamm Bowel Dis	2012	Cohort	United States	Countrywide	11	112,243	20,949	UC	61.6	5.0	5.0						183	163.0	12.0	139.4	186.6	Moderate
Jess[7]	Gastroenterology	2012	Cohort	Europe (Western)	Countrywide	29	385,608	47,374	IBD	40.3	55.0							338	87.7	4.8	78.4	97.0	Moderate
							130,391	*14,463*	*CD*	*35.7*	*57.0*							*70*	*53.7*	*6.4*	*41.1*	*66.3*	
							255,217	*32,911*	*UC*	*44.9*	*53.0*							*268*	*105.0*	*6.4*	*92.4*	*117.6*	
Jussila[10]	Scand J Gastroenterol	2013	Cohort	Europe (Western)	Countrywide	23	232,536	20,970	IBD									189	81.3	5.9	69.7	92.9	Moderate
							51,876	*4,983*	*CD*									*32*	*61.7*	*10.9*	*40.3*	*83.1*	
							180,660	*15,987*	*UC*									*157*	*86.9*	*6.9*	*73.3*	*100.5*	
Lakatos[48]	Inflamm Bowel Dis	2006	Cohort	Europe (Eastern)	7	11	8,564	723	UC	49.0	47.0	10.0		2.9	25.8			13	151.8	42.1	69.3	234.3	Moderate
Lakatos[32]	J Crohns Colitis	2011	Cohort	Europe (Eastern)	7	31	5,758	506	CD	31.5	50.4		31.0	1.8				5	86.8	38.8	10.7	162.9	Moderate
Lennard-Jones[34]	Gut	1990	Cohort	Europe (Western)	1	21	4,048	401	UC		42.6							22	543.5	115.9	316.4	770.6	Moderate
Lovasz[37]	J Gastroenterol Liver Dis	2013	Cohort	Europe (Eastern)	Regionwide	34	7,759	640	CD	28.0	49.8	11.0	38.4	0.9	34.5	47.2	7.7	6	77.3	31.6	15.4	139.2	Moderate
Manninen[11]	J Crohns Colitis	2013	Cohort	Europe (Western)	1	21	22,900	1,804	IBD	33.0	47.0	13.5	46.0	2.5	43.2			21	91.7	20.0	52.5	130.9	Moderate
							7,265	*551*	*CD*	*30.0*	*51.0*	*13.0*		*1.1*	*37.7*			*5*	*68.8*	*30.8*	*8.5*	*129.1*	
							15,635	*1,253*	*UC*	*34.0*	*45.0*	*13.1*		*3.2*	*49.4*			*16*	*102.3*	*25.6*	*52.2*	*152.4*	
Mellemkjaer[38]	Cancer Causes Control	2000	Cohort	Europe (Western)	Countrywide	16	22,875	2,645	CD		50.0							15	65.6	16.9	32.4	98.8	Moderate
Mizushima[39]	Digestion	2010	Cohort	Asia	1	20	4,248	294	CD	39.0	30.6				12.4			6	141.2	57.6	28.2	254.2	Moderate
Munkholm[40]	Gastroenterology	1993	Cohort	Europe (Western)	1	25	1,585	373	CD						5.6			2	126.2	89.2	-48.7	301.1	Moderate
Palli[41]	Gastroenterology	2000	Cohort	Europe (Western)	1	19	10,592	920	IBD									12	113.0	32.6	49.1	176.9	Moderate
							2,716	*231*	*CD*									*2*	*73.6*	*52.0*	*-28.4*	*175.6*	
							7,877	*689*	*UC*									*10*	*127.0*	*40.2*	*48.3*	*205.7*	
Pasternak[42]	Am J Epidemiology	2013	Cohort	Europe (Western)	Countrywide	11	304,992	38,772	IBD*	47.0	55.0		4.0			0.0	0.0	380	124.6	6.4	112.1	137.1	Moderate
Selinger[13]	Clin Gastroenterol Hepatol	2014	Cohort	Australia/New Zealand	2	15	13,423	881	IBD	31.5	53.1				38.4			29	216.0	40.1	137.4	294.6	Moderate
							5,417	*377*	*CD*	*29.0*	*59.1*				*37.4*			*5*	*92.3*	*41.3*	*11.4*	*173.2*	
							8,006	*504*	*UC*	*34.0*	*47.1*				*39.1*			*24*	*299.8*	*61.2*	*179.9*	*419.7*	
Van Schaik[44]	Gut	2012	Cohort	Europe (Western)	Countrywide	8	4,864	835	IBD*	43.0	57.0	2.9			29.0	0.0	0.0	9	185.0	61.7	64.1	305.9	Moderate
Venkataraman[45]	Australian J Gastroenterol Hepatol	2005	Cohort	Asia	1	25	4,901	532	UC		36.8	6.0	8.8		44.0			5	102.0	45.6	12.6	191.4	Moderate
Wandall[46]	Scand J Gastroenterol	2000	Cohort	Europe (Western)	Regionwide	25	8,101	801	UC	41.0	44.8	10.1	15.9		18.0			6	74.1	30.3	14.8	133.4	Moderate
Winther[47]	Clin Gastroenterol Hepatol	2004	Cohort	Europe (Western)	Regionwide	35	22,290	1,160	UC		53.4				54.0			13	58.3	16.2	26.6	90.0	Moderate
Yano[14]	J Gastroenterol Hepatol	2013	Cohort	Asia	1	25	10,552	770	CD	25.1	31.3	13.1			14.7			9	85.3	28.4	29.6	141.0	Moderate

Table 2: Characteristics of included studies of Leukemia in IBD

Author	Journal	Publication Year	Study Design	Region of Origin	Number of Sites	Study Duration (yrs)	Person Years	Number of Patients	Diagnosis	Mean Age (yrs)	Female (%)	Mean Disease Duration (yrs)	Surgery (%)	PSC (%)	Pancolitis (%)	Immunomodulator Use (%)	Biologic Use (%)	Observed Number of Leukemias	Incidence Rate (per 100,000 persons)	Standard Error	95% CI Lower Bound	95% CI Upper Bound	Bias Rating
Bernstein[23]	Cancer	2001	Case-control	Canada	Regionwide	14	41,005	5,529	IBD	39.0	54.5					0.0	0.0	7	17.1	6.5	4.4	29.8	Moderate
							21,340	*2,857*	*CD*	*36.3*	*59.0*					*0.0*	*0.0*	*3*	*14.1*	*8.1*	*-1.9*	*30.1*	
							19,665	*2,672*	*UC*	*41.7*	*50.0*					*0.0*	*0.0*	*4*	*20.3*	*10.2*	*0.4*	*40.2*	
Fraser[26]	Aliment Pharmacol Ther	2002	Cohort	Europe (Western)	Countrywide	35	55,388	1,578	IBD*	35.0	53.0				30.0	0.0	0.0	1	1.81	1.8	-1.7	5.4	Moderate
Jess[8]	Am J Gastroenterol	2013	Cohort	Europe (Western)	1	32	33,843	2,211	IBD		53.0				26.7	27.2		6	17.7	7.2	3.5	31.9	Moderate
							11,261	*774*	*CD*		*57.0*				*41.0*	*45.0*		*1*	*8.9*	*8.9*	*-8.5*	*26.3*	
							22,582	*1,437*	*UC*		*49.0*				*19.0*	*18.0*		*5*	*22.1*	*9.9*	*2.7*	*41.5*	
Lopez[19]	Clin Gastroenterol Hepatol	2014	Cohort	Europe (Western)	Countrywide	3	23,457	10,810	IBD*	40.0	53.0					0.0	0.0	0.5	2.13	3.0	-3.8	8.0	Moderate
Mellemkjaer[38]	Cancer Causes Control	2000	Cohort	Europe (Western)	Countrywide	16	22,875	2,645	CD		50.0							3	13.1	7.6	-1.7	27.9	Moderate
Mizushima[39]	Digestion	2010	Cohort	Asia	1	20	4,248	294	CD	39.0	30.6				12.4			0	0.0		0.0	3.7	Moderate
Palli[41]	Gastroenterology	2000	Cohort	Europe (Western)	1	19	10,592	920	IBD									2	19.0	13.4	-7.3	45.3	Moderate
							2,716	*231*	*CD*									*0*	*0.0*		*0.0*	*3.7*	
							7,877	*689*	*UC*									*2*	*25.4*	*18.0*	*-9.8*	*60.6*	
Winther[47]	Clin Gastroenterol Hepatol	2004	Cohort	Europe (Western)	Regionwide	35	22,290	1,160	UC		53.4				54.0			4	8.97	4.5	0.2	17.8	Moderate
Yano[14]	J Gastroenterol Hepatol	2013	Cohort	Asia	1	25	10,552	770	CD	25.1	31.3	13.1			14.7			3	28.4	16.4	-3.7	60.5	Moderate

Table 3: Characteristics of included studies of Lymphoma in IBD

Author	Journal	Publication Year	Study Design	Region of Origin	Number of Sites	Study Duration (yrs)	Person Years	Number of Patients	Diagnosis	Mean Age (yrs)	Female (%)	Mean Disease Duration (yrs)	Surgery (%)	PSC (%)	Pancolitis (%)	Immunomodulator Use (%)	Biologic Use (%)	Observed Number of Lymphomas	Incidence Rate (per 100,000 persons)	Standard Error	95% CI Lower Bound	95% CI Upper Bound	Bias Rating
Abbas[20]	Am J Gastroenterol	2012	Cohort	United States	Countrywide	11.0	352,429	32,039	UC	60.0	7.0					0.0	0.0	282	80.0	4.8	70.7	89.3	Moderate
Beaugerie[22]	Lancet	2009	Cohort	Europe (Western)	Countrywide	3.0	22,706	10,810	IBD		53.0				29.6	0.0	0.0	6	26.4	10.8	5.3	47.5	Moderate
							10,899	*5,153*	*CD*						*13.0*	*0.0*	*0.0*	*3*	*27.5*	*15.9*	*-3.6*	*58.6*	
							11,807	*5,657*	*UC*						*16.0*	*0.0*	*0.0*	*3*	*25.4*	*14.7*	*-3.3*	*54.1*	
Bernstein[23]	Cancer	2001	Case-control	Canada	Regionwide	14.0	41,005	5,529	IBD	39.0	54.5					0.0	0.0	16	39.0	9.8	19.9	58.1	Moderate
							21,340	*2,857*	*CD*	*36.3*	*59.0*					*0.0*	*0.0*	*9*	*42.2*	*14.1*	*14.6*	*69.8*	
							19,665	*2,672*	*UC*	*41.7*	*50.0*					*0.0*	*0.0*	*7*	*35.6*	*13.5*	*9.2*	*62.0*	
Chiorean[24]	Dig Dis Sci	2011	Case-control	United States	1	8.4	30,121	3,585	IBD									8	26.6	9.4	8.2	45.0	Moderate
							19,127	*2,277*	*CD*									*5*	*26.1*	*11.7*	*3.2*	*49.0*	
							10,994	*1,308*	*UC*									*3*	*27.3*	*15.8*	*-3.6*	*58.2*	
Farrell[25]	Gut	2000	Cohort	Europe (Western)	1	9.0	6,256	782	IBD*	44.1	52.0	10.0			26.0	30.0		4	64.0	32.0	1.3	126.7	Moderate
Fraser[26]	Aliment Pharmacol Ther	2002	Cohort	Europe (Western)	Countrywide	35.0	55,388	1,578	IBD	35.0	53.0				30.0	0.0	0.0	5	9.0	4.0	1.1	16.9	Moderate
							20,494	*584*	*CD*							*0.0*	*0.0*	*1*	*4.87*	*4.9*	*-4.7*	*14.4*	
							34,894	*994*	*UC*							*0.0*	*0.0*	*4*	*11.5*	*5.8*	*0.2*	*22.8*	
Herrinton[28]	Am J Gastroenterol	2011	Cohort	United States	Regionwide	13.0	67,867	16,023	IBD*		53.0					0.0	0.0	33	48.6	8.5	32.0	65.2	Moderate
Jess[8]	Am J Gastroenterol	2013	Cohort	Europe (Western)	1	32.0	33,843	2,211	IBD		53.0				26.7	27.2		15	44.3	11.4	21.9	66.7	Moderate
							11,261	*774*	*CD*		*57.0*				*41.0*	*45.0*		*7*	*62.2*	*23.5*	*16.1*	*108.3*	
							22,582	*1,437*	*UC*		*49.0*				*19.0*	*18.0*		*8*	*35.4*	*12.5*	*10.9*	*59.9*	
Jussila[10]	Scand J Gastroenterol	2013	Cohort	Europe (Western)	Countrywide	23.0	232,536	20,970	IBD									72	31.0	3.7	23.8	38.2	Moderate
							51,876	*4,983*	*CD*									*14*	*27.0*	*7.2*	*12.9*	*41.1*	
							180,660	*15,987*	*UC*									*58*	*32.1*	*4.2*	*23.8*	*40.4*	
Khan[31]	Gastroenterology	2013	Cohort	United States	Countrywide	10.0	199,046	36,891	UC	60.0	7.0					0.0	0.0	119	60.0	5.5	49.2	70.8	Moderate
Lakatos[32]	J Crohns Colitis	2011	Cohort	Europe (Eastern)	7	31.0	19,293	1,420	IBD	32.5	48.8		22.8	2.3	30.2	0.0	0.0	3	15.5	8.9	-2.0	33.0	Moderate
							7,093	*506*	*CD*	*28.5*	*50.0*		*41.3*	*1.8*	*35.9*	*0.0*	*0.0*	*1*	*14.1*	*14.1*	*-13.5*	*41.7*	
							12,830	*914*	*UC*	*36.5*	*47.6*		*4.2*	*2.7*	*24.4*	*0.0*	*0.0*	*2*	*15.6*	*11.0*	*-6.0*	*37.2*	
Lewis[35]	Gastroenterology	2001	Cohort	Europe (Western)	Countrywide	9.0	64,239	16,996	IBD	47.3	54.0					9.5		18	28.0	6.6	15.1	40.9	Moderate
							24,221	*6,605*	*CD*	*44.3*	*58.0*					*13.0*		*7*	*28.9*	*10.9*	*7.5*	*50.3*	
							40,018	*10,391*	*UC*	*50.3*	*50.0*					*6.0*		*11*	*27.5*	*8.3*	*11.2*	*43.8*	
Loftus[36]	Am J Gastroenterol	2000	Cohort	United States	2	53.0	6,662	454	IBD		24.0	14.9						1	15.0	15.0	-14.4	44.4	Moderate
							3,150	*216*	*CD*									*1*	*32.0*	*32.0*	*-30.7*	*94.7*	
							3,512	*238*	*UC*									*0*	*0.0*		*0.0*	*3.7*	
Mellemkjaer[38]	Cancer Causes Control	2000	Cohort	Europe (Western)	Countrywide	16.0	22,875	2,645	CD		50.0							4	17.5	8.8	0.4	34.7	Moderate
Mizushima[39]	Digestion	2010	Cohort	Asia	1	20.0	4,248	294	CD	39.0	30.6				12.4			0	0.0		0.0	3.7	Moderate
Palli[41]	Gastroenterology	2000	Cohort	Europe (Western)	1	19.0	10,592	920	IBD									7	66.0	24.9	17.1	114.9	Moderate
							2,716	*231*	*CD*									*1*	*36.8*	*36.8*	*-35.3*	*108.9*	
							7,877	*689*	*UC*									*6*	*76.2*	*31.1*	*15.2*	*137.2*	
Pasternak[42]	Am J Epidemiology	2013	Cohort	Europe (Western)	Countrywide	11.0	304,992	38,772	IBD*	47.0	55.0		4.0			0.0	0.0	46	15.1	2.2	10.7	19.5	Moderate
Van Domselaar[43]	J Gastroenterol Hepatol	2010	Cohort	Europe (Western)	1		8,563	911	IBD*	53.0	28.6	4.8						7	81.7	30.9	21.2	142.2	Moderate
Winther[47]	Clin Gastroenterol Hepatol	2004	Cohort	Europe (Western)	Regionwide	35.0	22,290	1,160	UC		53.4				54.0			2	17.9	12.7	-6.9	42.8	Moderate
Yano[14]	J Gastroenterol Hepatol	2013	Cohort	Asia	1	25.0	10,552	770	CD	25.1	31.3	13.1			14.7			0	0.0		0.0	3.7	Moderate

Figure 1: PRISMA Flowchart depicting the identification of studies, inclusion, and exclusion assessment

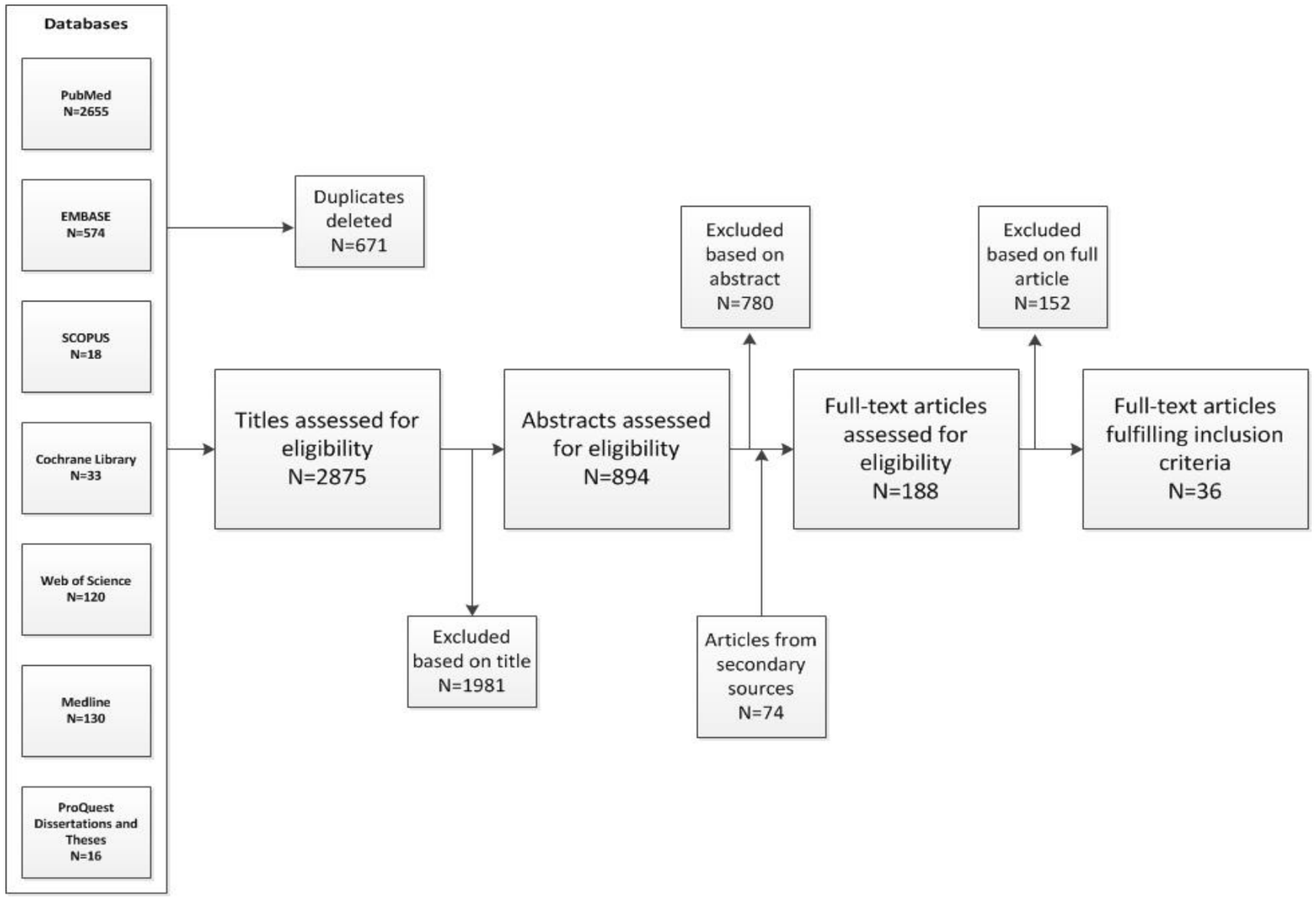
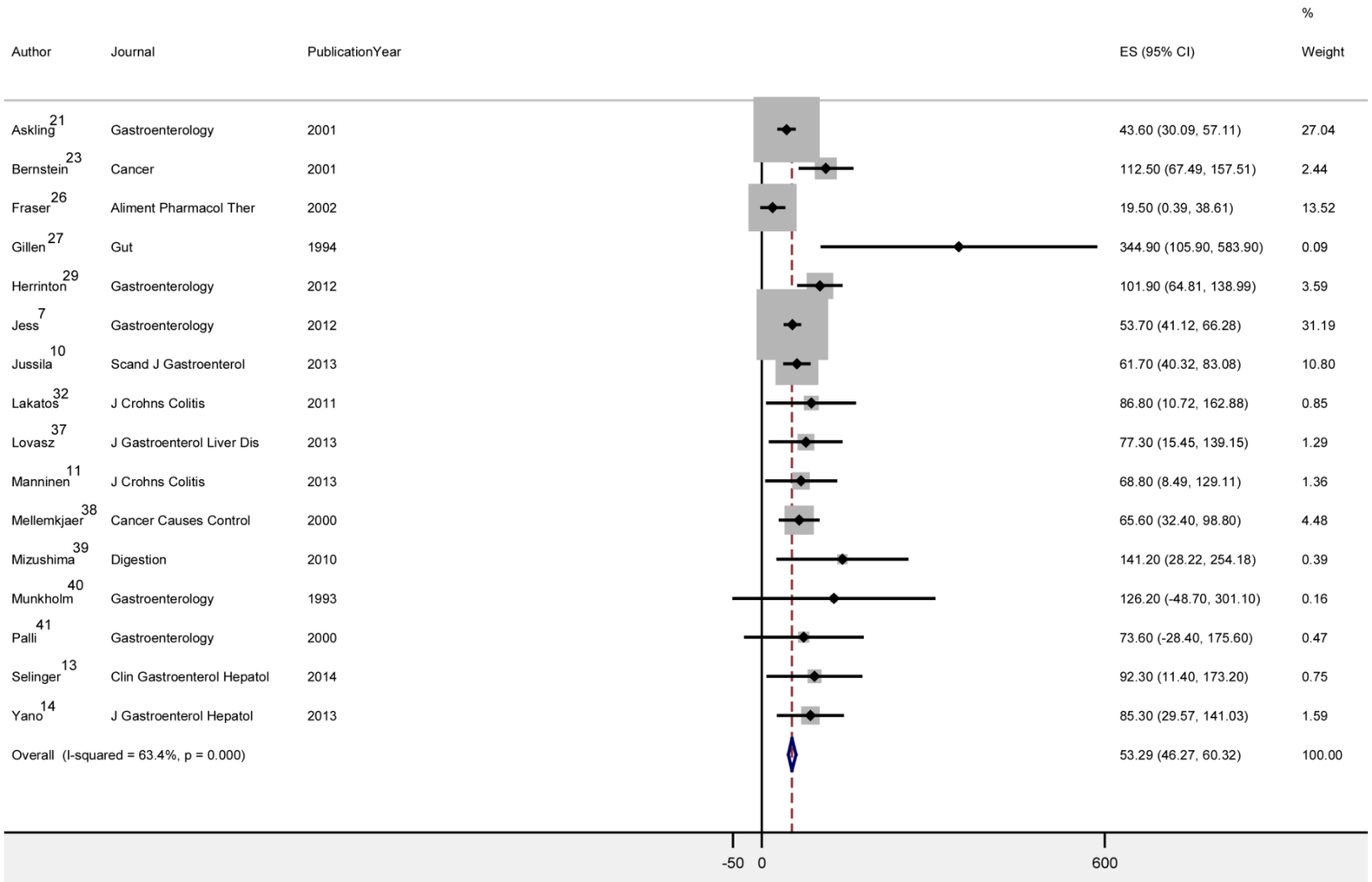


Figure 2: Incidence of colorectal cancer (CRC) in patients with Crohn's Disease (CD).



Each incidence estimate is presented followed by the 95% confidence intervals (CIs). Each square in the plot indicates the point estimate of the incidence. The diamond represents the summary incidence from the pooled studies. Error bars depict the 95% CIs.

Figure 3: Incidence of leukemia in patients with inflammatory bowel disease (IBD).

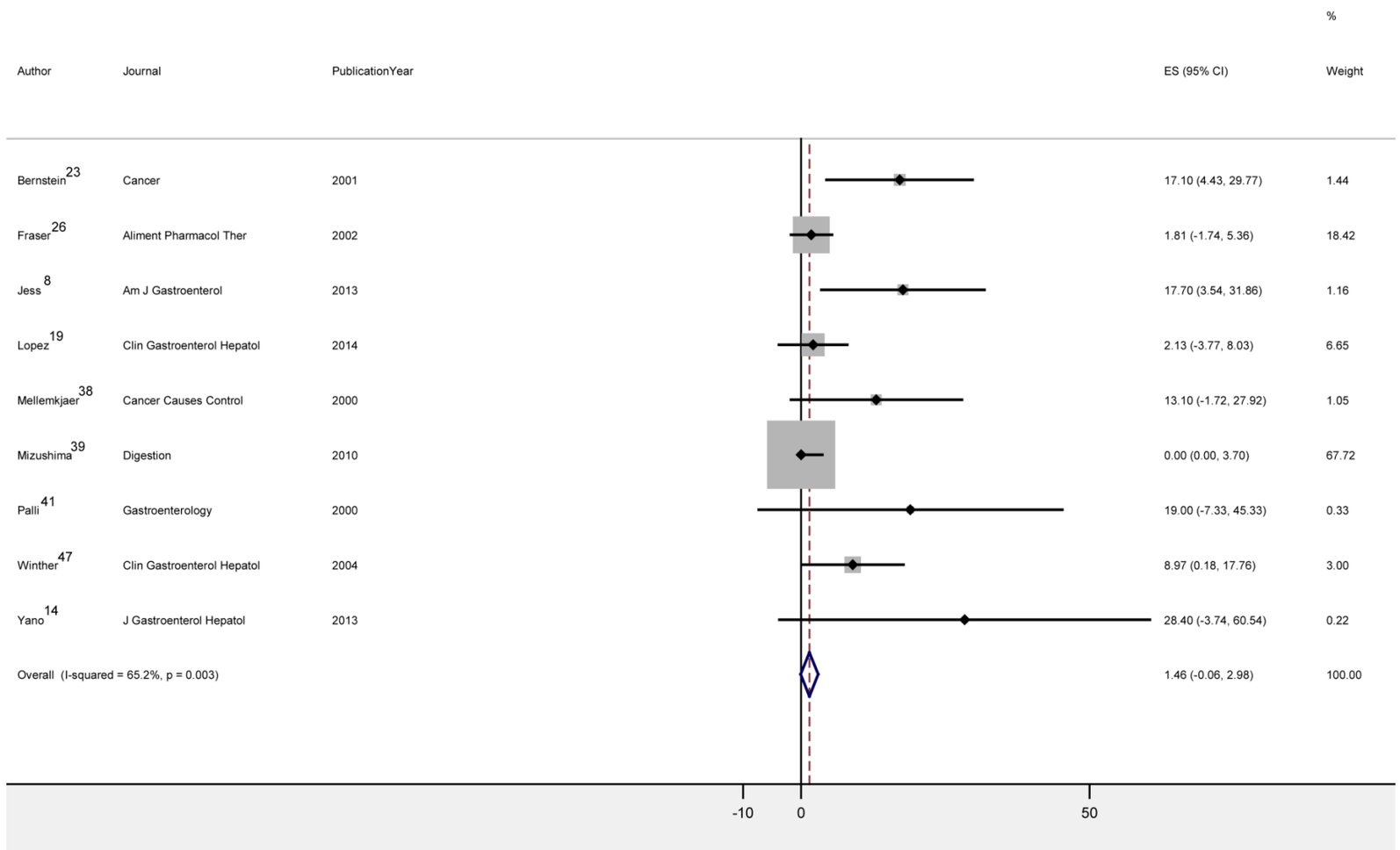
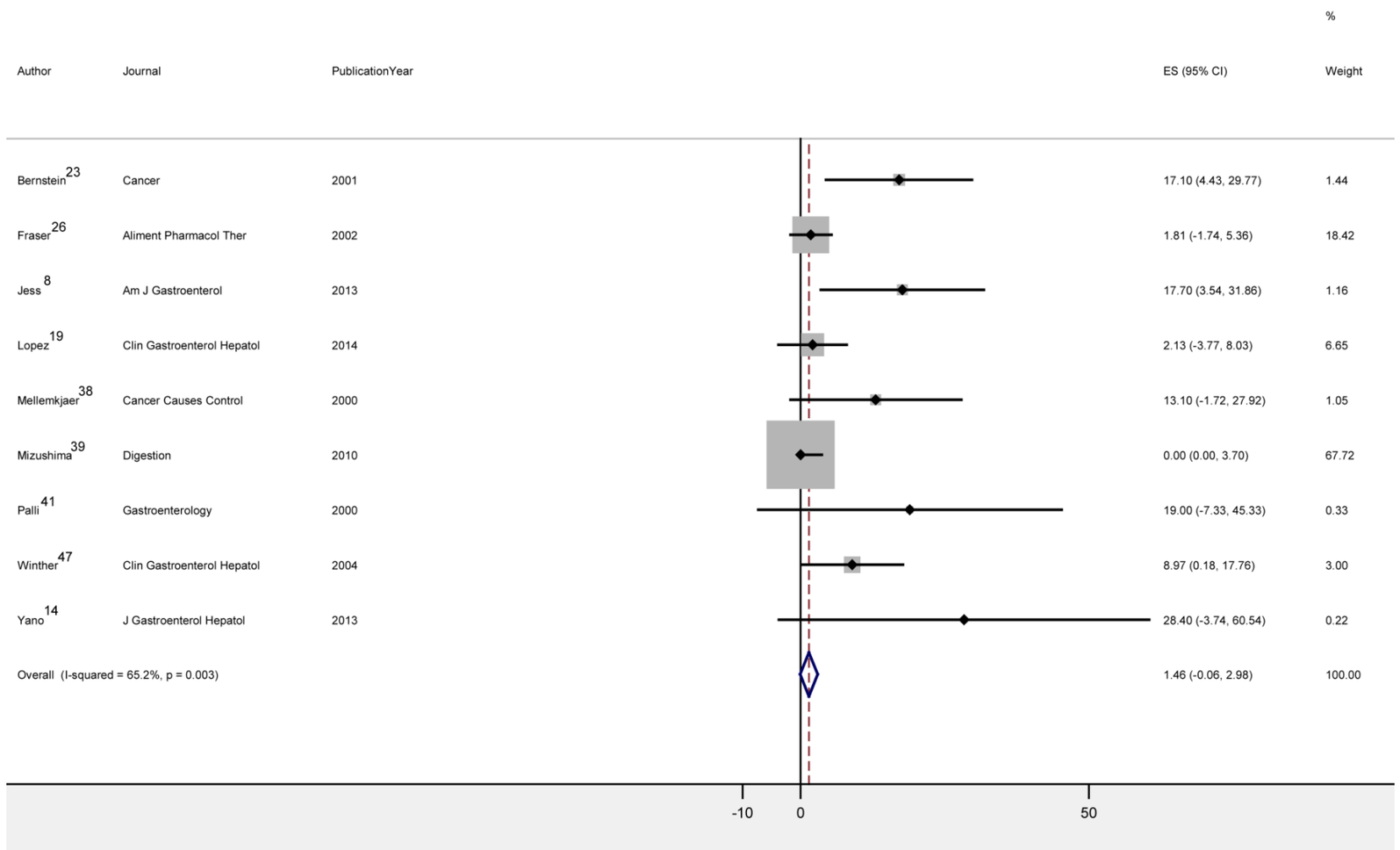


Figure 4: Incidence of lymphoma in patients with Crohn's Disease (CD).



Supplementary Table 1-Search Algorithms

PUBMED (results returned=2655)
((((((((((inflammatory bowel diseases[MeSH Terms]) OR inflammatory bowel disease[Title]) OR inflammatory bowel diseases[Title]) OR “crohn's disease”[Title]) OR “crohns disease”[Title]) OR “crohn disease”[Title]) OR “ulcerative colitis”[Title]) OR colitis[Title]) OR enterocolitis[Title]) OR ileocolitis[Title]) OR ileitis[Title])) AND ((((((((((((((((((Digestive System Neoplasms[MeSH Terms]) OR Abdominal Neoplasms[MeSH Terms]) OR Lymphoma[MeSH Terms]) OR Leukemia[MeSH Terms]) OR “colorectal cancer”[Title/Abstract]) OR “colorectal carcinoma”[Title/Abstract]) OR “colorectal tumors”[Title/Abstract]) OR “colorectal neoplasms” [Title/Abstract]) OR “colonic neoplasms”[Title/Abstract]) OR “rectal neoplasms”[Title/Abstract]) OR “rectal cancer”[Title/Abstract]) OR “colon cancer”[Title/Abstract]) OR lymphoma[Title/Abstract]) OR “hodgkin disease”[Title/Abstract]) OR “nonhodgkin lymphoma”[Title/Abstract]) OR lymphosarcoma[Title/Abstract]) OR leukemia[Title/Abstract]) OR leucocythaemia[Title/Abstract]) OR leucocythemia[Title/Abstract])))) AND adult) AND human
EMBASE (results returned=574)
('inflammatory bowel diseases':ti OR 'crohns disease':ti OR 'ulcerative colitis':ti OR colitis:ti OR enterocolitis:ti OR ileitis:ti OR ileocolitis:ti) AND ('digestive system neoplasms':ab,ti OR 'abdominal neoplasms':ab,ti OR lymphoma:ab,ti OR leukemia:ab,ti OR 'colorectal cancer':ab,ti OR 'colorectal carcinoma':ab,ti OR 'colorectal tumors':ab,ti OR 'colonic neoplasms':ab,ti OR 'rectal neoplasms':ab,ti OR 'rectal cancer':ab,ti OR 'colon cancer':ab,ti OR 'hodgkin disease':ab,ti OR 'nonhodgkin lymphoma':ab,ti OR lymphosarcoma:ab,ti OR leucocythaemia:ab,ti OR leucocythemia:ab,ti) AND (1990:py OR 1991:py OR 1992:py OR 1993:py OR 1994:py OR 1995:py OR 1996:py OR 1997:py OR 1998:py OR 1999:py OR 2000:py OR 2001:py OR 2002:py OR 2003:py OR 2004:py OR 2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py) AND ('adult') AND ('human')
SCOPUS (results returned=18)
(TITLE (inflammatory bowel disease* OR crohn* disease OR ulcerative colitis OR colitis OR enterocolitis OR ileitis OR ileocolitis) AND TITLE-ABS-KEY (digestive system neoplasm*) OR TITLE-ABS-KEY (abdominal neoplasm*) OR TITLE-ABS-KEY (lymphoma) OR TITLE-ABS-KEY (leukemia) OR TITLE-ABS-KEY (colorectal cancer) OR TITLE-ABS-KEY (colorectal carcinoma) OR TITLE-ABS-KEY (colorectal tumor*) OR TITLE-ABS-KEY (colorectal neoplasm*) OR TITLE-ABS-KEY (colonic neoplasm*) OR TITLE-ABS-KEY (rectal neoplasm*) OR TITLE-ABS-KEY (rectal cancer) OR TITLE-ABS-KEY (colon cancer) OR TITLE-ABS-KEY (hodgkin disease) OR TITLE-ABS-KEY (nonhodgkin lymphoma) OR TITLE-ABS-KEY (lymphosarcoma) OR TITLE-ABS-KEY (leucocythaemia) OR TITLE-ABS-KEY (leucocythemia)) AND PUBYEAR > 1989 AND TITLE-ABS-KEY (adult) AND TITLE-ABS-KEY (human)

COCHRANE LIBRARY (results returned=33)
"inflammatory bowel disease" OR "crohn's disease" OR "ulcerative colitis" OR colitis OR enterocolitis OR ileitis OR ileocolitis in Record Title and "digestive system neoplasm" OR "abdominal neoplasm" OR lymphoma OR leukemia OR "colorectal cancer" OR "colorectal carcinoma" OR "colorectal tumor" OR "colorectal neoplasm" OR "colonic neoplasm" OR "rectal neoplasm" OR "rectal cancer" OR "colon cancer" OR "hodgkin disease" OR "nonhodgkin lymphoma" OR lymphosarcoma OR leucocythaemia OR leucocythemia in Title, Abstract, Keywords and "adult"
WEB OF SCIENCE (results returned=120)
TI=(inflammatory bowel disease* OR crohns disease OR ulcerative colitis OR colitis OR enterocolitis OR ileitis OR ileocolitis) AND TS=(digestive system neoplasm* OR abdominal neoplasm* OR lymphoma OR leukemia OR colorectal cancer OR colorectal carcinoma OR colorectal tumor* OR colorectal neoplasm* OR colonic neoplasm* OR rectal neoplasm* OR rectal cancer OR colon cancer OR hodgkin disease OR nonhodgkin lymphoma OR lymphosarcoma OR leucocythaemia OR leucocythemia) AND TS=(adult) AND TS=(human OR patient OR man OR woman)
MEDLINE (results returned=130)
TI(inflammatory bowel disease* OR crohns disease OR ulcerative colitis OR colitis OR enterocolitis OR ileitis OR ileocolitis) AND TX(digestive system neoplasm* OR abdominal neoplasm* OR lymphoma OR leukemia OR colorectal cancer OR colorectal carcinoma OR colorectal tumor* OR colorectal neoplasm* OR colonic neoplasm* OR rectal neoplasm* OR rectal cancer OR colon cancer OR hodgkin disease OR nonhodgkin lymphoma OR lymphosarcoma OR leucocythaemia OR leucocythemia) AND TX(adult) AND TX(human)
ProQuest Dissertations and Theses (results returned=16)
ti(inflammatory bowel disease* OR crohns disease OR ulcerative colitis OR colitis OR enterocolitis OR ileitis OR ileocolitis) AND all(digestive system neoplasm* OR abdominal neoplasm* OR lymphoma OR leukemia OR colorectal cancer OR colorectal carcinoma OR colorectal tumor* OR colorectal neoplasm* OR colonic neoplasm* OR rectal neoplasm* OR rectal cancer OR colon cancer OR hodgkin disease OR nonhodgkin lymphoma OR lymphosarcoma OR leucocythaemia OR leucocythemia) NOT all((mouse OR rat OR murine))

CHAPTER 4: EDUCATIONAL NEEDS OF PATIENTS WITH INFLAMMATORY BOWEL DISEASE (IBD) AND NON-ADHERENCE TO MEDICAL THERAPY-A QUALITATIVE STUDY

Abstract

Background: Patients with inflammatory bowel disease (IBD) are at risk for serious complications when their disease is poorly managed. Patient non-adherence to medical therapy contributes to suboptimal outcomes, but may be modified through improved education. The primary aim of this study is to identify educational needs, barriers and factors associated with non-adherence, to assist with future development of educational resources for this patient population.

Methods: Eighteen IBD patients and ten IBD providers were recruited. Semi-structured interviews were conducted and a qualitative framework approach used to identify patient educational needs, barriers to obtaining information, and factors associated with non-adherence with medical therapy.

Results: Prevention of IBD symptoms and factors contributing to development of IBD were the most frequently identified patient educational needs. Both providers and patients identified diet and nutrition, as well as access to general information about IBD, as important areas of education. Common barriers to obtaining or conveying information for patients and providers included: information oversaturation, ineffective provider communication skills, and lack of provider time. Several factors that impact patient comprehension and decision making were also identified. Providers most frequently believed that patient non-adherence is associated with lack of current symptoms or denial of their chronic condition.

Conclusions: Our findings highlight several deficits in knowledge in IBD patients. We also identify factors associated with IBD patient comprehension, decision making, and non-adherence to therapy that can be targeted with educational resources to improve adherence.

Introduction

Inflammatory bowel disease (IBD) is a group of autoimmune disorders of the gastrointestinal tract, most commonly ulcerative colitis (UC) and Crohn's disease (CD). The impact of IBD can be debilitating to those afflicted, and adverse effects from medical and/or surgical therapy may further contribute to a reduction in quality of life. It is known that poorly controlled disease increases the risk for serious and often irreversible negative outcomes including death.[1-5] One factor that contributes to suboptimal disease control and complications is patient non-adherence to medical therapy.

Individuals may elect to forego medical and/or surgical therapy due to inconvenience, cost of therapy, lack of understanding, or fear of side effects from therapy. Inconvenience and cost of therapy are reasons for non-adherence to treatment, but are difficult to address due to limited mutability of either factor. Fear of adverse effects from therapy and lack of understanding of available treatment options are contributing factors to non-adherence that may be amenable to change. Education specific to IBD, its effects, and its management, can potentially increase patient adherence and improve outcomes for these patients.[6]

Current evidence suggests that many individuals with IBD lack the desired information about their disease[7-10] Specific areas of interest to IBD patients include:

prevention and management of IBD symptoms, complications related to IBD, long term prognosis, risk of cancer and mortality, alternative therapies, risks from pharmacotherapy, research and potential new therapies, as well as fertility.[7-12] These information needs were identified through surveys administered via varied modes to specific patient populations (e.g. newly diagnosed); however to our knowledge an intensive qualitative study in a diverse IBD patient population specifically exploring this topic has not been published. The primary aim of this study is to determine the perceived educational needs of IBD patients (i.e. the information about issues that a patient desires to understand such as their disease process, their prognosis, and their therapeutic options), and to identify areas that providers believe patient understanding is critical. This information can be used to develop novel educational resources to improve patient adherence to therapy. A further aim is to describe the barriers to patients obtaining information and those experienced by providers when conveying information to patients. In addition, we aim to identify barriers and facilitators to patient comprehension, decision making, and adherence to therapy recommendations.

Materials and Methods

We identified and interviewed ten providers who care for patients with IBD at the University of Washington Medical Center [UWMC] and its affiliates, Harborview Medical Center [HMC, a safety net hospital] and Veteran's Administration Puget Sound Health Care System [VA], in Seattle, WA, in 2015. HMC is a public hospital that serves many patients with lower education and income levels compared to other healthcare facilities in the area (including UW). In addition, many patients are transient and for varied

social reasons do not receive consistent medical care. Providers (MD, ARNP, RN) were identified through publicly available online directories and contacted via email.

Eighteen patients with IBD who receive care at UWMC or HMC were also recruited and interviewed. Patients were identified through their providers (the same providers that were asked to participate in the study), and asked for their verbal consent to be contacted by the lead researcher (CW). All interviewees provided oral assent prior to being interviewed. Patient participants were oversampled from HMC due to known differences in education level, income level, and other patient characteristics (such as consistency of care, patient non-adherence to therapy,) between the institutions.

Two interview guides were utilized for this study, one for the patient population and one for the providers. We developed our patient interview guide with feedback from a patient with a non-IBD related autoimmune condition, a gastroenterologist, and a patient advocate. The interview guide used with providers elicited information regarding the type of information the provider would like to convey to their IBD patients, the difficulties that they experienced in the past in communicating with their patients, and the factors they believed were associated with patient understanding, decision making, and non-adherence to therapy recommendations. [Supplemental Appendix 1] The interview guide used with patients elicited information regarding their level of confidence with their knowledge of IBD, the type of information the participants would like to receive from their providers, and past difficulties in communicating with their providers. [Supplemental Appendix 2]

Interviews lasted approximately thirty minutes, and were conducted with the lead researcher (CW) at a location of the participant's choosing, either via phone or in-person. All interviews were recorded with permission and transcribed. Provider interviews were conducted until reaching our predetermined target of ten interviews. Although there was no existing formal analytical method for sample size determination in qualitative research available, published literature estimated that twelve interviews provided approximately 92% of the information desired, and when utilizing knowledgeable individuals (such as the case with IBD providers) ten or less participants was often sufficient.[13,14] Patient interviews were conducted until reaching information saturation.[13,14] Information saturation was defined as a lack of new themes emerging, and was determined by the primary researcher (CW).

Responses to the interview questions formed the basis for the qualitative analysis. We utilized a framework approach to guide our data analysis methodology. Framework analysis is a method in which the data were interpreted by searching for associations, patterns, themes, concepts, and explanations in the data.[14,15] Each interview was independently coded by two researchers (CW and MM), the themes identified, and the data reviewed until consensus. We revised and finalized our coding structure after completion of the coding for the first and second interviews for each group (providers and patients). Data were collected, stored, and analyzed using ATLAS.ti (ATLAS.ti Scientific Software Development GmbH Version 7.0). Means with standard deviations were calculated for continuous participant characteristics, and proportions for categorical measures. Statistical analyses of descriptive characteristics

were conducted using Stata MP 13.0 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

Ethical Considerations

The study was determined to be exempt from review by the University of Washington's Human Subjects Division in Seattle, WA. All respondents were assured of confidentiality, and informed that there participation was voluntary. Interviewees were compensated a nominal amount ($10.00 Starbucks© gift card) for their involvement.

Results

Table 1 outlines the characteristics of the participants. 78% of patient participants received their IBD care at HMC, and the majority were male (61%). Their mean age was 31.6 years (+/- 9.8 years) and their average disease duration was 8.6 years (+/- 7.2 years). Among the provider participants, 50% primarily practiced at UWMC and there was equal representation of men and women. Their average length of experience treating patients with IBD was 5.7 years (2.3).

Educational Needs

The most frequently conveyed educational need by IBD patients was how to prevent symptoms related to their IBD (n=12). [Table 2]

> *"… being able to piece together what's going to make my life as livable as it can be and my disease as manageable as it will be."*

In addition, information related to the prevention or cause of IBD was recurrently expressed by respondents (n=11).

> *"It would be really interesting to me to find out what's the mechanism that causes the inflammatory process in the first place."*

Expected medication effects and/or information related to medication management (n=9), as well as natural remedies for IBD (n=9), were both common themes discussed.

> *"Making sure that there are some better options out there in case the meds that I am using are not working." [a patient discussing the importance of information regarding medication management]*

> *"I feel like there is more that can be done than just putting someone on medication." [a patient expressing their desire for natural therapeutic options to treat their IBD]*

Diet and nutritional concerns were especially important to many patients, regardless of whether they were newly diagnosed or had been living with IBD for many years (n=8).

> *"I wish I knew about diet more than anything else."*

Other respondents thought that information about IBD in general, including its natural progression and the effects of the inflammatory process, would be valuable (n=5). In addition, some patients were especially concerned about their own prognosis (n=4). Lastly, a few participants were interested in information about new therapies and technological advancements related to IBD (n=2), and how to access resources to obtain their medical care and/or IBD medication (n=1).

> *"…it would be interesting to hear more about new techniques of diagnosis, and new treatment options from my doctors."*

Table 2 also details critical concepts for IBD patients to understand as identified by providers. The importance of adherence to medication (n=13) and an understanding of IBD in general (n=13) were the two most commonly expressed areas that providers feel are crucial for IBD patients to understand.

> *"…if you take the medications and the medications prove to be efficacious, their [the patient's] quality of life long term is just as if they didn't have the disease." [a provider explaining how important adherence to medication is for patient quality of life]*

"…it's the basic natural progression of this disease as far as how bad it could be or it could get." [a provider discussing the importance of patient understanding regarding IBD in general and how it can progress]

Providers also identified the follow-up plan as a critical area for patient education (n=9).

" …that the plan is in place that is agreeable to them and agreeable to the physician. That they understand what that plan is and where they are going."

Other respondents felt that ensuring patients know the provider's contact information is essential, in order to avoid situations such as unnecessary emergency room visits (n=2). Furthermore, diet and nutrition (n=1); the necessity of taking personal responsibility for one's own disease management (such as completing necessary lab work) (n=1); and understanding that the provider is the patient's advocate (n=1), were all conveyed as crucial patient comprehension areas.

"It is important for them [patients] to know that I am their advocate, and that they should share with me the struggles that they have, whether it is disease related or struggles with the side effects of medications, or even financial concerns about affording therapy."

Barriers to Desired Information

IBD patients and their providers identified numerous barriers to obtaining or conveying information that fulfilled patient educational needs. [Table 3] Patients most frequently identified the variable quality of online information as a barrier to obtaining information (n=12); whereas providers most commonly identified information oversaturation (n=18).

"I don't trust anything that is on the internet." [a patient speaking in reference to the variable quality of online information available to them]

"Telling them [the patient] you have inflammatory bowel disease, there are two different kinds, here are all of the treatments, here are the risk factors, and adverse effects related to the treatments….that is information in a deluge for them [the patients]." [a provider explaining how information saturation is a barrier to information for many patients]

Additional barriers identified by patients included information oversaturation (n=9), ineffective provider communication skills (n=6), and lack of provider time to fully answer patient questions (n=5).

> *"But you can't really take anything in…you shut down." [a patient discussing how it is difficult to process too much information]*

> *"I had to go on WebMD and figure out what this disease is that this lady [the provider] is telling me I have." [a patient expressing frustration with the provider's communication skills]*

> *"They have little interest in me-they literally give you 15 minutes of an appointment and outside of that they don't want to talk to you. Then they move on to the next person." [a patient explaining how lack of provider time is a barrier to information]*

Other barriers conveyed by patients include: the inability to personalize the information (n=2); information complexity (n=2); erroneous information (n=1); a lack of consolidated information (n=1) and logistical constraints, such as inability to physically find the information (n=1).

> *"It [the available information] is generic; it's not exactly for you." [a patient describing the barrier of inability to personalize the information]*

> *"Not being a trained professional, it is hard to decipher the information." [a patient explaining how information complexity is a barrier]*

Providers also acknowledged that their lack of time was a significant barrier to information for patients (n=11).Barriers specifically related to the healthcare system, such as difficulties with patient access to care, were also noted (n=11).

> *"I think the most limiting factor is time." [a provider expressing lack of their time as a barrier to information for their patients]*

> *"The difficulty is having patients be able to get into the system and talk about their issues." [a provider discussing the difficulties some patients experience accessing care]*

Lack of consolidated information (n=7); logistical constraints (n=6); lack of provider support staff (n=6); information complexity (n=5); inability to personalize information (n=2); ineffective provider communication skills (n=1); erroneous information (n=1); and language (n=1), were other barriers to information that providers conveyed.

> *"You can usually get the information somewhere, but the problem is, to be able to find the perfect resource in one place. It's very challenging." [a provider discussing how the lack of consolidated information is not only a barrier for patients but for providers as well]*

> *"We don't have someone specifically that supports IBD patients here, unlike some other IBD clinics. They [specialized support staff] are very up on their IBD because that is all that they do." [a provider explaining how a lack of specialized support staff is a barrier for their patients]*

> *"Sometimes the information, because it is FDA mandated, puts fear in patients that is not necessary." [a provider conveying how information complexity can be a barrier to information for patients]*

Factors associated with Patient Comprehension, Decision Making, and Non-Adherence

Table 4 summarizes the identified factors that may impact patient comprehension and patient decision making.

<u>Comprehension</u>

Providers frequently indicated that patient educational level (n=13), as well as social and cultural factors (n=13), are associated with patient comprehension of information. In addition, language fluency plays a substantial role in patient understanding (n=11).

> *"the literacy level of some patients, even information from the CCFA [Crohn's and Colitis Foundation of America], is too high of a literacy level for them to understand." [a provider explaining how education impacts patient comprehension]*

> *"We do have a lot of people who need translators, where English is not their first language, I think that it is even harder for them [the patients] to process all of the information." [a provider discussing how language influences patient understanding]*

Other patient factors conveyed by providers as influencing patient comprehension included: age (n=8); level of interest (n=8); health literacy (n=7); absorption time (n=5); disease severity (n=3); anxiety and/or fear (n=2); learning or mental disabilities (n=2); and mental health (n=1).

> *"Some people are less interested in the details of what is going on, and then some people are a lot more interested, and want to know a lot more about the details of their care." [a provider expressing how patient interest impacts understanding]*

Patients identified fewer factors associated with information comprehension than providers. These factors included: age (n=1); interest (n=1); absorption time (n=1); and disease severity (n=1).

> *"I was really, really ill, so was relatively incoherent, and was not in the ideal state of mind to be given that sort of information." [a patient explaining how disease severity plays a role in the comprehension of information]*

<u>Decision making</u>

Providers identified a number of potential factors that may influence patient decision making. Balancing the short term versus the long term effects of therapy and/or the disease was the most frequently noted concern (n=5).

> *"I think that there are some misconceptions about the side effects of treatment, but also having long term, uncontrolled disease, even if they [the patient] don't have symptoms."*

Trust in the patient's provider (n=4); patient insurance coverage and/or the cost of treatment (n=4); and patient past experiences (n=2) were also commonly discussed.

> *"They [the patients] have a tough time trusting that we [the providers] are going to give them good care, and that they are going to be safe." [a provider discussing how it is especially challenging for patients who are transitioning from pediatric care to adult care, and how trust can influence the patient's decision making]*

> *"Usually it is based on what the insurance has determined that the patient is going to get." [a provider explaining how the patient's insurance often dictates the patient's treatment course]*

A few providers explained how educational level (n=1); socioeconomic factors (n=1); and patients feeling that they lack alternative treatment choices (n=1) all influence the patient's decision making process.

> *"I think that some of the fear is that there is nothing out there that is going to help ." [a provider discussing how a patient believing that lacking alternative treatment choices can influence decision making]*

Patients frequently discussed how their past experiences (n=7) and balancing the short term versus long term effects from therapy and/or disease (n=4) influenced their decision making.

> *"I have the risk of getting cancer, I have the risk of death, and it brings me to ask, which one is worse, really?" [a patient conveying how taking into account the shorter term potential effects from unmanaged disease versus the longer term potential risks from therapy impact their decision making]*

Other patients expressed that trust in their provider (n=3) and feeling as if there are no alternative choices (n=2) significantly impact their decision making.

> *"I have no choice." [a patient expressing frustration at their perceived lack of choice regarding receiving medication for their IBD]*

<u>Patient non-adherence</u>

Table 5 describes the provider identified factors associated with patient non-adherence. The most frequently expressed issue related to patient non-adherence by providers was a patient's lack of current symptoms or denial of their chronic condition (n=12).

> *"If you are not feeling well, I think it is in the forefront of your mind, but if those patients are in remission and are doing well, I think that they are more likely to not go to an infusion or miss a day of medication."*

Social or cultural factors (n=10); past side effects or fear of side effects (n=9); logistical factors (n=9); complicated treatment courses (n=8); financial considerations (n=7); and

lack of patient understanding regarding IBD (n=7) were other commonly noted themes regarding patient non-adherence to treatment recommendations.

> *"There are so many other things that they [the patients] have to worry about in their life that it is hard to remember when to take their pills." [a provider discussing how social factors influence patient adherence]*

> *"Patients think oh well, I can't afford it so I just won't do it, so they stop and hope for the best." [a provider conveying how insurance and cost impact patient adherence]*

> *"It is difficult to bridge that gap of, even if you can't see the damage that is being done it is really important for you to maintain your medication course." [a provider explaining how it is difficult for some patients to truly understand their disease and its effects]*

Some providers felt that patient lack of understanding in general (n=2); forgetfulness (n=2); mental health issues (n=1); embarrassment by their disease and/or its treatment (n=1); desire for natural therapy (n=1); fear and/or anxiety (n=1); and lost or stolen medication (n=1) were other factors that influence patient adherence.

> *"They [the patients] are scared because these are scary medications."*

Discussion

The perspectives of the patients and providers interviewed for this study demonstrate several key issues related to IBD patient educational needs and the barriers to obtaining desired information currently experienced by IBD patients. We also identified some of the factors perceived to be involved with patient comprehension, decision making, and non-adherence to provider treatment recommendations. First, despite the current availability of many educational resources for IBD patients, there remain a number of unmet educational needs for this population. Patients want to know how to prevent the symptoms of their disease, receive information regarding the cause of IBD, and have more discussion around the disease in general. A number of patients

also expressed an interest in diet and nutrition, specifically how to maximize nutritional status given their disease. These patient concerns overlapped with provider-identified critical understanding areas, particularly concerning diet and nutrition and information regarding IBD in general. As such, these areas may be targets for novel educational resources to improve patient understanding.

Exploring existing barriers to patient understanding may also assist in developing needed educational resources. Many patients are utilizing the internet as one of their primary information sources, and the variable quality of online information available is a significant barrier. Patients and providers both identified information oversaturation, ineffective provider communication skills, and lack of provider time as additional information barriers for IBD patients. These results highlight the need for providers to consider both the amount and format of information presented to patients at any given time, particularly for newly diagnosed patients and for those who are severely ill. Furthermore, mechanisms to increase the provider time available to IBD patients, such as the availability of specialized support staff, are crucial to patient education and understanding.

Our findings are similar to those in the published literature, particularly in reference to the patients' identified educational needs. Information on the prevention of symptoms, complications, causes, long term prognosis and/or outcomes, effects and/or risks from therapy, and alternative treatments were identified as educational needs both by our subjects and in prior studies.[7-12,16,17] Education regarding diet and nutrition was identified by many of our patients as an area where they desired additional information; however this was not a previously identified concern in this population. This

dissimilarity may be specific to our population or an emerging area of educational need that has yet to be fully explored. Our study is unique in its evaluation of both patient educational needs and areas where providers feel that patient understanding is critical.

Factors that are associated with patient comprehension and decision making are essential considerations when discussing strategies to meet the educational needs of IBD patients. Providers frequently recognized patient educational level, social and cultural factors, and language as determinants of patient comprehension. Providers also identified patient age, level of interest, health literacy, and absorption time as important considerations. Patients agreed that their age, interest, absorption time, and disease severity all play a role in understanding. In regards to decision making, balancing the short term versus the long term effects of therapy and/or IBD, trust in the patient's provider, and the patient's past experiences were commonly identified by both patients and providers as factors that significantly influence patient decision making. Therefore, it is critical to ensure that educational resources are appropriate for varying health literacy levels, and age groups. In addition, resources must be available in multiple languages and be developed by individuals with cultural awareness of the groups being targeted. The other factors, such as patient absorption time and provider trust, are the responsibility of the provider to assess and facilitate.

Identifying issues associated with patient non-adherence that are amenable to change is also important for targeting educational interventions. Issues that providers most commonly identified as associated with patient non-adherence included: lack of current symptoms, denial of their chronic condition, social or cultural factors, past side effects or fear of side effects, logistical factors, complicated treatment regimens,

insurance or cost considerations, and lack of full understanding of their disease. Many of these concerns are responsive to modification through education, specifically education targeted towards IBD, its effects, and its management.

Patient self-management programs are effective interventions for individuals with other chronic diseases such as diabetes, and could be used as models for use in the IBD population. These programs are typically led by trained lay leaders, as well as health care professionals. They have a group based format and content areas include: symptom management; understanding medication use; management of feelings such as fear, anger, and frustration; solving health-related problems; and communication with providers.[18-20] There is minimal research into the effectiveness of self-management interventions in IBD; however the available evidence suggests that self-management programs are associated with a number of positive outcomes including fewer hospital stays and improved psychological well-being in IBD patients.[19] Self-management programs tailored towards IBD patients are able to not only meet many of the patient educational needs identified in our study, but are able to circumnavigate the barriers to information and patient adherence identified here. These programs can also take into account the varied factors associated with patient comprehension and decision making. Thus, they are potentially effective educational interventions that warrant further study.

It is known that poorly controlled disease in IBD patients increases the risk for serious negative outcomes, and that a significant contributing factor to suboptimal disease management is patient non-adherence to medical therapy. Our findings highlight existing knowledge deficits among the IBD patient population, and the barriers to IBD patient comprehension and decision making. In addition, we identified many

potential influences to patient non-adherence that might be amenable to change through education. Exploration of these areas will assist in developing targeted educational resources. Tailoring these resources to patients at higher risk for non-adherence may maximize their impact upon patient understanding, decision making, and outcomes.

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Tables and Appendices

Table 1: Patient and provider demographic characteristics

	Patients (N=18)		Providers (N=10)
Institution-no. (%)		**Institution-no. (%)**	
UWMC	4 (22.2)	UWMC	5 (50.0)
HMC	14 (77.8)	HMC	3 (30.0)
VA	0 (0.0)	VA*	2 (20.0)
Interview mechanism-no. (%)		**Interview mechanism-no. (%)**	
In-person	8 (44.4)	In-person	10 (100.0)
Phone	10 (55.6)	Phone	0 (0.0)
Sex-no. (%)		**Sex-no. (%)**	
Men	11 (61.1)	Men	5 (50.0)
Women	7 (38.9)	Women	5 (50.0)
Education level-no. (%)		**Role-no. (%)**	
High School	3 (16.7)	Fellow (MD)	2 (20.0)
Technical School	1 (5.5)	Attending (MD)	4 (40.0)
College	14 (77.8)	Nurse Practioner (NP)	1 (10.0)
Age (years)-mean (SD)	31.6 (9.8)	Registered Nurse (RN)	3 (30.0)
Disease duration (years)-mean (SD)	8.6 (7.2)	**Length of IBD experience (years)-mean (SD)**	5.7 (2.3)
Past surgical history-no. (%)	7 (38.9)		
Current biologic therapy -no. (%)	15 (83.3)		
Current immunomodulator therapy-no. (%)**	14 (77.8)		
Current steroid therapy-no. (%)	3 (16.7)		
Current mesalamine/sulfasalazine therapy-no. (%)	3 (16.7)		
Past biologic therapy-no. (%)	6 (33.3)		
Past immunomodulator **therapy-no. (%)	3 (16.7)		
Past steroid therapy-no. (%)	11 (61.1)		
Past mesalamine/sulfasalazine therapy-no. (%)	5 (27.8)		

UWMC-University of Washington Medical Center
HMC-Harborview Medical Center
VA-Veteran's Administration Puget Sound Health Care System
SD-standard deviation
*The VA is an affiliate of the University of Washington and its providers are University of Washington faculty
**Azathioprine, 6-mercaptopurine, or methotrexate

Table 2: Patient identified educational needs and provider identified critical understanding areas for IBD patients

Patient Identified Educational Needs	
Educational Need	**Frequency of occurrence**
The prevention of symptoms related to IBD	12
The prevention of IBD or information related to the cause of IBD	11
Expected medication effects and/or information related to medication management	9
Natural remedies for IBD	9
Diet and nutrition*	*8*
IBD in general*	*5*
Disease prognosis	4
New therapies and technological advancements related to IBD	2
Accessing resources to obtain medical care and/or IBD pharmacotherapy	1
Provider Identified Critical Understanding Areas for Patients	
Critical Understanding Area	**Frequency of occurrence**
The importance of adherence to medication	13
IBD in general*	13
The patient's individual follow up plan	9
Provider contact information	2
Diet and nutrition*	1
The necessity of taking personal responsibility for one's own disease management	1
The provider is the patient's advocate	1

**Italicized and bolded text indicates educational needs/critical understanding area identified by both patients and providers*

Table 3: Patient and provider identified barriers to desired information sources

Information Barrier	Patient identified	Provider identified
The variable quality of online information available	12	7
Information oversaturation	9	18
Ineffective provider communication skills	6	1
Lack of provider time	5	11
The inability to personalize the information	2	2
Information complexity	2	5
Erroneous information	1	1
Lack of consolidated information	1	7
Logistical constraints	1	6
Barriers that exist within the healthcare system	0	11
Lack of support staff	0	6
Language barriers	0	1

Table 4: Factors that impact patient comprehension and decision making

Patient comprehension	Patient identified	Provider identified
Patient education level	0	13
Social and cultural factors	0	13
Language fluency	0	11
Patient age	1	8
Patient interest	1	8
Patient health literacy	0	7
Patient absorption time	1	5
Patient disease severity	1	3
Patient anxiety and/or fear	0	2
Patient learning or mental disabilities	0	2
Patient mental health	0	1
Patient decision making	**Patient identified**	**Provider identified**
Short term versus long term effects of therapy and/or disease	4	5
Provider trust	3	4
Insurance coverage and/or cost of treatment	0	4
Patient past experiences	7	2
Feeling as if there are no alternative choices	2	1
Patient educational level	0	1
Patient socioeconomic factors	0	1

Table 5: Provider identified factors associated with patient non-adherence

Factor	Frequency of occurrence
The patient feels well or is in denial of their chronic condition	12
Social or cultural factors	10
The patient has experienced side effects or is fearful of side effects	9
Logistical factors	9
The treatment course is complicated	8
Lack of insurance, cost, or the patient has experienced an insurance change	7
The patient has a lack of understanding regarding their disease	7
The patient has a lack of understanding in general	2
The patient is forgetful	2
The patient has mental health issues	1
The patient is embarrassed by their disease and/or its treatment	1
The patient desires natural therapy	1
The patient is fearful or has anxiety	1
Lost or stolen medication	1

Supplemental Appendix 1

Provider Questions

Question #1

How do you usually convey information about therapeutic and/or surgical treatment options to patients?

Question #2

Please describe any existing information sources that you use to convey information about treatment options to patients.

Question #3

Do you feel that you have access to adequate resources in order to effectively convey information to patients about therapeutic and/or surgical treatment options?

Question #4

If the answer to question #3 is no, what type of information do you feel is lacking?

Question #5

If the answer to question #3 is yes, is there any type of information that you feel would add to your practice?

Question #6

Do you feel that your patients understand you when you communicate information about their disease and/or therapeutic options?

Question #7

If the answer to question #6 is no, what do you think would help your patients better understand you?

Question #8

Do you find that there are certain characteristics of patients who do or do not understand their treatment information? If so, please describe these characteristics.

Question #9

How do you assess your patients' understanding of the information that you convey?

Question #10

What do you feel is the most important information for you to convey to your patients and for them to understand?

Question #11

Why do you think patients are not adherent to treatment recommendations?

Question #12

How do you feel that patient adherence can be improved?

Question #13

Do you find that there are forms of communication that are more effective in facilitating patient understanding? If so, which forms of communication do you find the most effective?

Question #14

What formats of patient communication tools do you find the most effective?

Question #15

How long have you been treating IBD patients?

Question #16

Do you learn better if you hear the information, read the information, or do something yourself?

Supplemental Appendix 2

Patient Questions

Question #1

How much do you feel you know about your IBD?

Question #2

What are you most interested in learning about your IBD?

Question #3

What concerns or worries (if any) do you have about your health?

Question #4

What concerns or worries (if any) do you have about your IBD treatment?

Question #5

When were you diagnosed with IBD?

Question #6

What specific problems (if any) are you having now?

Question #7

Do you learn better if you hear the information, read the information, or do something yourself?

Question #8

What medications for your IBD have you taken or are you currently taking?

Question #9

Who do you ask or where do you look for information if you have questions about your IBD or your medications?

Question #10

Are there sources or formats of information that are more or less helpful to you in understanding your IBD or medications? If so, please describe these further.

Question #11

Have you had surgery for your IBD?

Question #12

If the answer to question 11 is yes, have you had more than one surgery for your IBD?

Question #13

How many years of schooling have you completed?

Question #14

What is your age?

CHAPTER 5: CONCLUSION

Overview

It is crucial for patients with inflammatory bowel disease (IBD) to have proper medical management in order to avoid serious complications from their disease. It is also imperative for providers to have easy access to accurate and timely information regarding the risk of adverse events from IBD and its therapies, and to effectively communicate these risks to patients so that they can make informed decisions about their health and treatment. The three studies presented as part of this dissertation begin to address some of the limitations in our current knowledge regarding IBD and its therapies. In addition, we identify the educational needs of IBD patients and their providers, as well as discuss some of the barriers and factors associated with non-adherence, to assist with the future development of educational resources for this patient population.

IBD therapy and infection

In Chapter 2 we show, through the use of a network meta-analysis of randomized controlled trials (RCTs), that no IBD treatment strategy confers a higher odds of serious infection than another. As prior evidence regarding the magnitude of risk of serious infections due to IBD pharmacotherapy is conflicting,[1-5] our findings provide a better understanding of one of the most clinically significant risks of interest associated with IBD treatment. Of specific interest, we provide support for the safety of dual immunosuppressive therapy with biologic medications and immunomodulators, which is reassuring given the need for this treatment strategy for patients who are at high risk of antibody formation and loss of response to some biologic therapies. In addition, we

found no evidence of a higher odds of serious infection from the newly available biologic therapies, such as vedolizumab and ustekinumab, compared to the anti-tumor necrosis factor (anti-TNF) biologic agents for which we have longer term safety data. Given the growing number of IBD patients who have lost response or who are intolerant to anti-TNFs, this information can be used to assist patients and providers considering treatment with one of these newer therapies.

IBD and cancer

In Chapter 3, we provide updated incidence estimates for colorectal cancer (CRC), leukemia, and lymphoma within the IBD patient population. We specifically attempt to quantify the underlying risk of these malignancies excluding the effects of IBD pharmacotherapy, given that these medications may increase cancer risk. CRC incidence is hypothesized to be higher in IBD patients than in the general population, most likely due to a combination of chronic inflammation and genetic factors.[6-8] With better surveillance strategies and new treatment options for IBD, updated estimates of the magnitude of risk of CRC are needed. Some studies have also suggested that IBD patients may be at higher risk of lymphoproliferative disorders such as lymphoma and leukemia; however the underlying risk of these cancers without the effects of immunomodulating medications is unclear.[9-13] We performed a systematic review and meta-analysis of the published literature in order to obtain updated estimates for each malignancy, and found that the overall incidence of these malignancies in the IBD population are low and similar to estimates from worldwide general population level studies. These findings can be used by providers when determining appropriate cancer

surveillance strategies for their IBD patients, as well as provide a better understanding of the risk of these cancers from IBD for both patients and providers.

Educational needs of IBD patients and providers

Chapter 4 presents the findings from a qualitative study of IBD patients and their providers. We used semi-structured interviews and a qualitative framework approach to identify patient educational needs, barriers to obtaining information, and factors that may be associated with non-adherence to medical therapy. Our findings highlight several deficits in knowledge among IBD patients including how to prevent IBD symptoms and factors contributing to the development of IBD. We found agreement between providers and patients that information regarding diet and nutrition, as well as general information about IBD, are important areas of education and may be targets for novel educational resources to improve patient understanding. Common barriers to information that were identified by patients and providers include information oversaturation, ineffective provider communication skills, and lack of provider time. These results highlight the need for providers to consider how they present information to patients, as well as how important mechanisms to increase provider time are to patient education and understanding. We also explored some of the factors that are associated with patient comprehension and decision making, as well as issues associated with patient non-adherence. Many of the discussed concerns are responsive to modification through education, and we propose that patient self-management programs that are similar to effective interventions in other chronic disease populations could be used as models for the IBD population.

Contribution

The strength of this dissertation comes from the novelty of the paper described in Chapter 2 in its direct comparison of multiple therapies on the association of a significant risk of interest, including combinations of therapies for IBD, that have never been previously explored in this manner. In addition, we present the results of an exhaustive literature search and statistical summary of published information in order to provide updated incidence estimates for three malignancies of clinical interest in Chapter 3. We conclude with a summary of information crucial to the future development of educational tools to facilitate patient understanding and adherence to medical therapy, potentially improving the long term outcomes for these individuals. Despite the strength of the work presented here, this research is not without limitations which are discussed in detail in the preceding chapters.

Implications and future directions

Based on the principles of shared decision making, we hypothesize that providing the evidence compiled here regarding the risks associated with IBD and its treatment, as well as providing a foundation of information from which future educational tools can be developed, will facilitate patient decision making, support patients in understanding their disease prognosis, and improve adherence to medical therapy. Given our knowledge that patients with poorly managed disease are at the highest risk for serious complications from IBD, we hope that dissemination of this research will begin to overcome the barriers to appropriate treatment that arise from fear or misunderstanding regarding the disease and its treatment. We also hope that the

information presented can assist providers in guiding patients towards their best therapeutic options in order to maximize patient quality of life for those living with IBD.

This dissertation provides the foundation for future work in this area. Specifically, additional studies to quantify the incremental increased risk of cancer from IBD pharmacotherapy, and examination of subpopulations of IBD patients that may be at higher risk of infection and malignancy from their disease and/or therapy (e.g. older adults) would advance the current state of knowledge. In addition, the information obtained from the qualitative study will be used in combination with the results of the body of work describing the risks of infection and malignancy to develop novel educational tools targeting the areas of knowledge deficit identified. Following development of these resources, validation within varied IBD patient populations and determination of how they impact patient knowledge and adherence to therapeutic recommendations will be undertaken.

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