Journal of Crohn's and Colitis, 2020, 1–10
doi:10.1093/ecco-jcc/jjaa050
Advance Access publication July 10, 2020
Original Article

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Combined Biologic and Immunomodulatory Therapy is Superior to Monotherapy for Decreasing the Risk of Inflammatory Bowel Disease-Related Complications

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Abstract

Background and Aims: The combination of infliximab and azathioprine is more efficacious than either therapy alone for Crohn's disease [CD] and ulcerative colitis [UC]. However, it is uncertain whether these benefits extend to real-world clinical practice and to other combinations of biologics and immunomodulators.

Methods: We collected health administrative data from four Canadian provinces representing 78 413 patients with inflammatory bowel disease [IBD] of whom 11 244 were prescribed anti-tumour necrosis factor [anti-TNF] agents. The outcome of interest was the first occurrence of treatment failure: an unplanned IBD-related hospitalization, IBD-related resective surgery, new/recurrent corticosteroid use or anti-TNF switch. Multivariable Cox proportional hazards modelling was used to assess the association between the outcome of interest and receiving combination therapy vs anti-TNF monotherapy. Multivariable regression models were used to assess the impact of choice of immunomodulator or biologic on reaching the composite outcome, and random effects generic

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inverse variance meta-analysis of deterministically linked data was used to pool the results from the four provinces to obtain aggregate estimates of effect.

Results: In comparison with anti-TNF monotherapy, combination therapy was associated with a significant decrease in treatment ineffectiveness for both CD and UC (CD: adjusted hazard ratio [aHR] 0.77, 95% confidence interval [CI] 0.66–0.90; UC: aHR 0.72, 95% CI 0.62–0.84). Combination therapy was equally effective for adalimumab and infliximab in CD. In UC azathioprine was superior to methotrexate as the immunomodulatory agent (aHR = 1.52 [95% CI 1.02–2.28]) but not CD (aHR = 1.22 [95% CI 0.96–1.54]).

Conclusion: In an analysis of a database of real-world patients with IBD, combination therapy decreased the likelihood of treatment failure in both CD and UC.

Key Words: Anti-TNF; combination therapy; inflammatory bowel disease; adverse outcomes; infliximab; adalimumab; azathioprine; thiopurine; methotrexate

What is already known about this subject?

Combination therapy with azathioprine and infliximab is superior to infliximab monotherapy for induction and maintenance of remission in Crohn's disease and ulcerative colitis

The effectiveness of combination therapy in real world practice is unclear, or with different combinations of anti-TNF agents and immunomodulators

What are the new findings?

Patients on combination therapy are ~30% less likely to experience IBD-related hospitalization, surgery, corticosteroid use, or switching between therapies than those using monotherapy for both Crohn's disease and ulcerative colitis

Combination therapy is effective for both infliximab and adalimumab, while azathioprine appears to be preferred over methotrexate, especially for ulcerative colitis

How might it impact clinical practice in the foreseeable future?

This study confirms the positive impact of combination therapy outside of randomized controlled trials and specialty clinic settings

This should encourage physicians to promote the use of combination therapy in suitable patients in their IBD practice.

1. Introduction

The prevalence of inflammatory bowel disease [IBD] in Canada is 0.7% and is forecasted to rise to 1% of the population by 2030.[1] Most up-to-date guidelines on the medical management of Crohn's disease [CD] and ulcerative colitis [UC] recommend the use of combination therapy with an anti-tumour necrosis factor [anti-TNF] agent and an immunomodulatory drug (thiopurines or methotrexate [MTX]) over a drug from either class alone.[2,3] These recommendations are largely based on the results of the SONIC study in CD and the SUCCESS-UC randomized controlled trials.[4,5] In both of these trials, the specific combination of azathioprine [AZA] and infliximab [IFX] was shown to be superior to either IFX or the thiopurine AZA as monotherapy in inducing clinical and endoscopic remission, and in maintaining remission in CD. However, there are no randomized controlled trials [RCTs] that have convincingly demonstrated that the benefits of combination therapy extend to other anti-TNF biological agents. Furthermore, the only RCT [COMMIT] which compared combination therapy with MTX and IFX to IFX alone did not show a significant difference in the likelihood of attaining clinical remission, although MTX was shown to raise anti-TNF drug levels and to reduce immunogenicity.[6]

In practice, clinicians often extend the findings of SONIC and SUCCESS-UC to other anti-TNF agents, particularly adalimumab [ADL], under the presumption that the same effects would be observed. Furthermore, clinicians may use MTX in place of AZA as the combination agent with an anti-TNF despite there being less evidence of its efficacy, largely because of fears of haematological and malignant complications with thiopurine use.[7–9] However, there are limited experimental or real-world data to be certain whether the benefits of combination therapy apply to other combinations of anti-TNF therapy and immunomodulators [IMs].

We have previously demonstrated using only data from the Canadian province of Manitoba [population 1.35 million] that combination therapy with a biologic and an IM in CD was associated with a reduced likelihood of treatment failure, defined as any of: an unplanned IBD-related hospitalization, IBD-related resective surgery, new/recurrent corticosteroid use or changing to another anti-TNF10. However, the study was not sufficiently powered to evaluate the benefit of combination therapy in UC, or specific combinations of anti-TNFs and IMs.

Therefore, we decided to perform a distributed epidemiological analysis by applying the same study design in population-based cohorts from four Canadian provinces in order to increase the statistical power and thus better address the following questions:

1] Do the benefits of combination therapy extend to UC in the real-world setting?
2] Does the choice of anti-TNF agent [IFX or ADL] or IM [thiopurine vs MTX] impact outcomes?

2. Methods

2.1. Study setting and population

This study was performed through a retrospective analysis of routinely collected health care utilization data in the four western Canadian provinces of British Columbia, Alberta, Saskatchewan and Manitoba, which encompassed a total population of just over 11 million people in 2016. Each of the four provinces captures data from nearly 100% of registered residents, and captures all instances of inpatient hospitalization, all inpatient and most of the outpatient physician–patient interactions, and all outpatient dispensations

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Table 1. Characteristics of provincial datasets

	British Columbia [BC]	Alberta [AB]	Saskatchewan [SK]	Manitoba [MB]
Population [2015]	4 848 055	4 067 175	1 098 352	1 278 365
Number of IBD patients	37 902	27 333	8314	10 636
CD	16 601	13 970	4764	5233
UC	18 960	9932	3550	5403
Years of data available	1990–2015	2008–2015	1998–2016	1984–2016
Case finding definition	Four outpatient visits within 2 years or two inpatient visits within 2 years.	2 hospital admissions, 4 practitioner claims, or 2 ambulatory care/ER-based medical contacts within 2 years	≥5 physician contacts or CIHI-DAD records within 2 years of health coverage, and ≥3 separate contacts with <2 years of coverage	≥5 hospitalizations and/or physician contacts for IBD

CD, Crohn's disease; CIHI-DAD, Canadian Institute of Health Information-Discharge Admissions Database; ER, emergency room; IBD, inflammatory bowel disease; UC, ulcerative colitis.

of prescription medication. In each province, all cases of CD and UC were identified using previously validated case finding definitions.[11–13] A complete summary of the composition of each province's healthcare utilization database and the internally validated IBD case finding definition is shown in Table 1. These datasets do not contain information on health-associated behaviours [smoking, alcohol use, etc], the use of over-the-counter medications, or the results of laboratory, endoscopic, radiographic or pathology testing.

2.2. Identification of anti-TNF monotherapy and combination therapy cohorts

Within the cohort of patients with a diagnosis of IBD, we identified all those who received at least one new dispensation for an anti-TNF medication. All patients who had at least two healthcare contacts for any condition other than IBD where anti-TNF therapy is frequently used were excluded [rheumatoid arthritis, psoriasis, ankylosing spondylitis, etc.]. We also excluded all those who were first registered with their provincial health agency after the availability of anti-TNF medication or with less than 1 year of continuous registration prior to their initial receipt of anti-TNF medication to exclude prevalent users who had moved to that jurisdiction. For the timeframe of data availability for this study, IFX and ADL were the only anti-TNF agents used for IBD in Canada.

2.2.1. Exposure of interest

The main exposure variable was whether an IM [a thiopurine or MTX] was used concomitantly [combination therapy] or not used concomitantly [monotherapy] at the onset of anti-TNF therapy. For a patient to be assigned to the combination therapy group, they had to meet one of the following criteria:

1] If there was no IM dispensation in the 120 days prior to anti-TNF initiation: the first IM dispensation following the initial anti-TNF must occur within 30 days following the start of anti-TNF therapy
2] If there was an IM dispensation in the 120 days prior to anti-TNF initiation, then the next IM dispensation must occur within 120 days following the most proximate IM dispensation occurring prior to anti-TNF initiation

All other patients who did not meet one of the above criteria were assigned to the monotherapy group, even if IMs were dispensed later in the course of therapy. This design allows our exposure of interest [combination vs monotherapy] to function as an intent-to-treat variable. This schema is pictured in Supplementary Figure 1.

2.2.2. Determination of duration of active anti-TNF therapy

The duration of the treatment effect for anti-TNFs was assumed to be 56 days for each dispensation of IFX, and 14 days for each pre-filled syringe of ADL dispensed. Continuous use was assumed as long as there was no more than 90 days between the expected last date of treatment effect for an anti-TNF dispensation and the subsequent anti-TNF dispensation. If there were no subsequent anti-TNF dispensations, or if more than 90 days transpired between the end of treatment effect of one anti-TNF dispensation and the subsequent anti-TNF dispensation, then the discontinuation date was assigned as the day the treatment effect ended. Subjects were censored at death, migration out of the province [and therefore loss to follow-up in health administrative data] or end of longitudinal data availability. These use concepts are illustrated in Supplementary Figure 2.

2.2.3. Outcomes of interest

The main outcome of interest was time to development of treatment failure, which was defined as any of the following events occurring after anti-TNF initiation:

1] Acute unplanned [non-elective] admission to hospital for greater than 24 h with a most-responsible diagnosis of IBD. A most-responsible diagnosis is the diagnosis which is designated by the admitting physician to be most responsible for the inpatient hospital stay.
2] Resective intestinal surgery [see Appendix A for a list of surgical codes]
3] Corticosteroid use: if there is no corticosteroid dispensation within 16 weeks prior to anti-TNF initiation, then any systemic corticosteroid dispensation occurring more than 14 days following the date of anti-TNF initiation. Corticosteroid use within 14 days following the start of anti-TNF therapy was ignored, as this may represent part of the initial induction: if there was a corticosteroid dispensation within 16 weeks prior to the start of anti-TNF initiation, then any corticosteroid dispensed ≥16 weeks following anti-TNF initiation was considered relevant. To be considered significant, at least 500 mg of prednisone or equivalent needed to be dispensed over a 16-week period.

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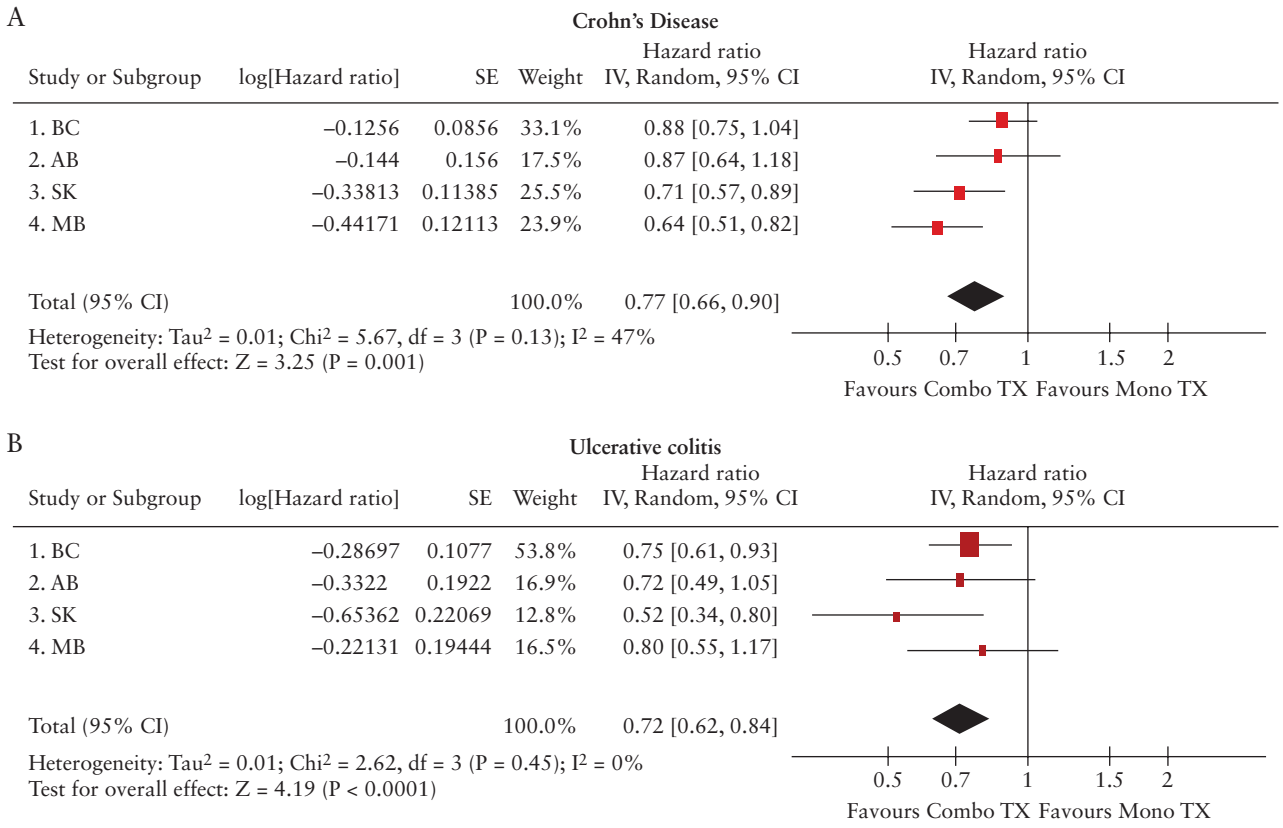

Figure 1. Association between use of combination therapy and the hazard of any treatment failure.

Budesonide use was not considered to be a marker of treatment ineffectiveness, as it is often used in clinical scenarios that are distinct from when traiditional corticosteroids are used. We did run an exploratory analysis using only data from Manitoba to determine if including budesonide use as an outcome would lead to a meaningful difference in the outcome.

4] Use of an alternative anti-TNF agent [i.e., from IFX to ADL or vice versa]. Other biological agents such as vedolizumab, ustekinumab and tofacitinib were not available in Canada during the study period ending in March 2016

For an event to be considered treatment-associated, it must have occurred either prior to anti-TNF discontinuation or within 90 days following the date of anti-TNF discontinuation. Discontinuation *without* the occurrence of one of the aforementioned treatment ineffectiveness outcomes was *not* considered to be treatment failure, although all data following discontinuation are censored.

2.2.4. Statistics

Within each of the included provincial datasets, we used multivariable Cox proportional hazards models to assess the relationship between the exposure of interest [use of any combination therapy vs any anti-TNF monotherapy] and both the composite outcomes, and each of its individual component outcomes. Controlling variables included in the analysis were age [<25, 25–64, 65+ years] sex, disease duration [<3 vs 3+ years], use of any of the following medications within 1 year prior to starting anti-TNF therapy [serotonin-selective reuptake inhibitors, opioids, corticosteroids] and IBD-related hospitalization within 1 year of anti-TNF initiation, and Charlson-Deyo score. These variables were selected as they could be easily discerned from the available data, and may potentially be associated with underlying disease severity. We also created models on restricted datasets on the subcohorts of CD using IFX and those with CD using ADL to determine whether the effect of combination therapy was influenced by the choice of anti-TNF agent [IFX vs ADL]. Last, models restricted to all CD and all UC using combination therapy was created to determine if the effect of selecting MTX over a thiopurine on the risk of developing the composite outcome. Adjusted hazard ratios [aHR] and 95% confidence intervals [CI] were reported for all models in each province.

As we could not pool data from the four provincial datasets on the individual patient level due to healthcare privacy laws, we instead conducted a meta-analysis of the aggregate outcomes from each of the provinces using random-effects models, with the effect of each province being weighted in proportion to the inverse variance of the standard error.[14] Heterogeneity between individual provinces was assessed using the I2 statistic and all meta-analyses were performed using RevMan 5.4 [Cochrane Collaboration].

3. Results

A total of 78 413 individuals met the case finding definition for IBD [40 568 CD, 37 845 UC], of whom 11 244 [14.3%] were dispensed at least one anti-TNF dispensation [7679 IFX, 3565 ADL]. Among those prescribed an anti-TNF, 8129 [72.2%] had CD [5050 IFX, 3079 ADL] and 3115 [27.8%] had UC [2629 IFX, 486 ADL]. In total, 5.9% of patients first received anti-TNF when under the age of 18 years. The characteristics of anti-TNF users stratified by province are shown in Table 1.

Patient demographics and disease characteristics are displayed in Table 2. Overall, 4411 [39.2%] anti-TNF users met the criteria for using concomitant IM therapy, with no difference seen between CD and UC [39.1% vs 39.8%]. Thiopurines were used as concomitant therapy in 84% of those with CD, and 92% of those with UC. Doses

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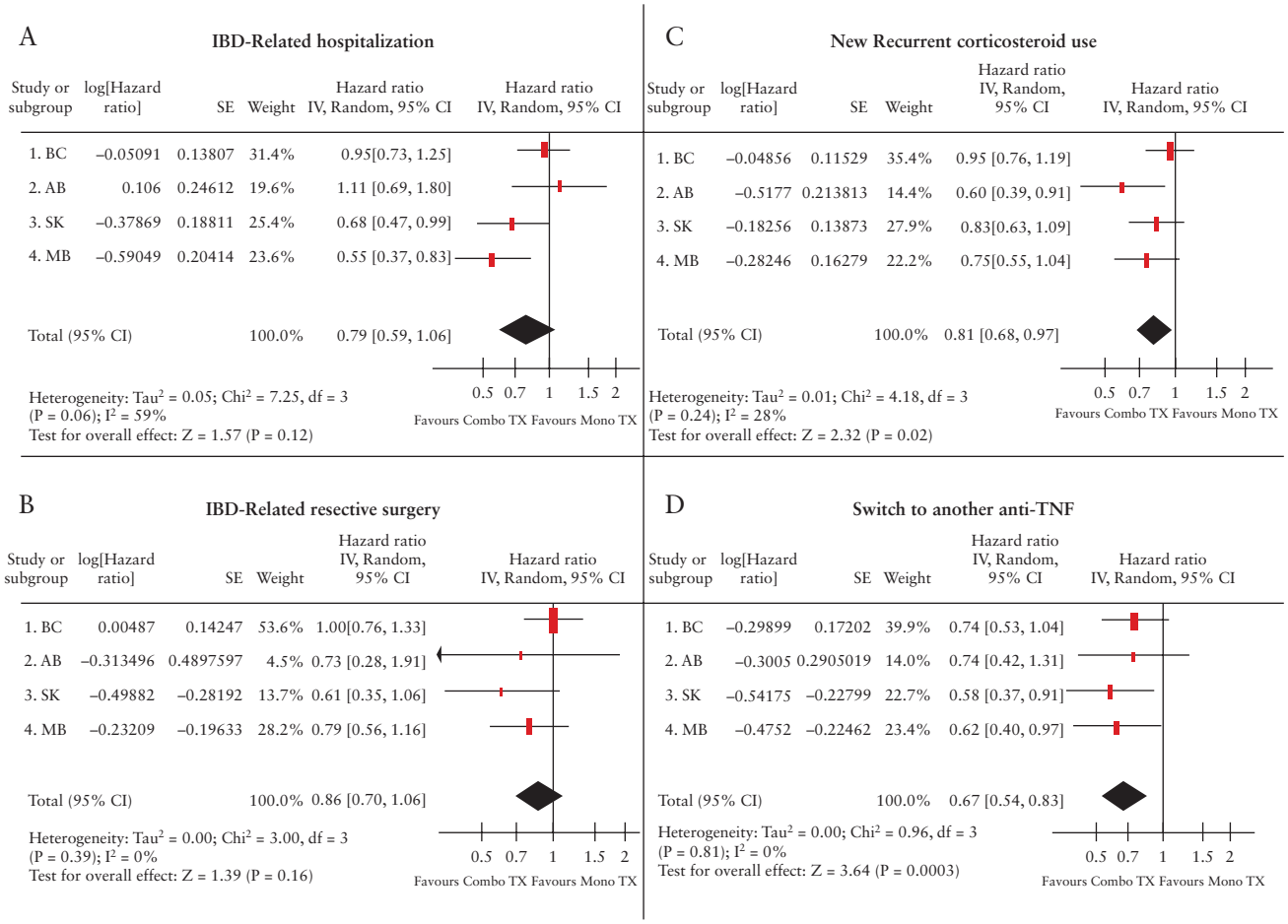

Figure 2. Association between use of combination therapy and the hazard of individual treatment failure outcomes [Crohn's disease].

exceeding 75 mg of AZA [or 37.5 mg of mercaptopurine] were used by 94.2% of patients using combination therapy in Manitoba.

In the pooled analyses of patients, combination therapy was associated with a decreased hazard of the composite outcome [i.e. hospitalization, surgery, corticosteroid use, or switch of anti-TNF] in both patients with CD [aHR 0.77, 95% CI 0.66–0.90] and UC [aHR 0.72, 95% CI 0.62–0.84] [Figure 1]. The effect of combination therapy on each of the individual outcomes is shown in Figure 2 for CD, and Figure 3 for UC; combination therapy was associated with a statistically significant decreased likelihood of most of the individual outcomes for both CD and UC compared with monotherapy, except for a few outcomes where the confidence interval crossed 1.

Among patients with CD, those who used MTX as the immunomodulator over thiopurines had a numerically greater hazard of treatment failure, but this did not reach statistical significance [aHR 1.22, 95% CI 0.96–1.54]. In the UC cohort, the use of MTX over thiopurines as combination therapy was associated with an increased hazard for the composite outcome [aHR 1.53, 95% CI: 1.01–2.28] [Figure 4]. In CD, the thiopurine-based combination therapy was associated with a significant decrease in the hazard of treatment failure both for CD [aHR 0.76, 95% CI: 0.67–0.86] and for UC [aHR: 0.70, 95% CI: 0.59–0.82]. There was no significant benefit seen for MTX-based combination therapy for CD [aHR 0.97, 95% CI: 0.76–1.24] or UC [aHR: 1.00, 95% CI: 0.68–1.46], although the confidence intervals were wide due to lower rates of MTX use [Figure 4]. Inclusion of budesonide used as a marker of treatment ineffectiveness in CD did not change the magnitude of this effect when assessed using data from the province of Manitoba.

4. Discussion

In this study of over 11 000 anti-TNF users, the use of a concomitant IM at the time of anti-TNF initiation was associated with a statistically significant and clinically meaningful reduction in the likelihood of treatment failure. Combination therapy led to statistically significant reductions in the need for corticosteroids and biological switch among CD patients, and the need for corticosteroids and IBD-related hospitalization among UC patients, although all individual measures of treatment failure showed a strong trend towards combination therapy being protective. These data suggest that the benefits of combination therapy observed in clinical trials extend to the real-world setting. Evidence is required from other jurisdictions to confirm these findings.

In CD, combination therapy was superior to monotherapy for both IFX and ADL. This finding is consistent with the SONIC RCT that showed IFX with AZA was superior to IFX alone. However, the benefits of using concomitant immunomodulators have not been demonstrated as clearly for ADL as they have for IFX. A small RCT showed that the combination of ADL and AZA was superior to ADL alone for promoting mucosal healing at 26 weeks but not at 52 weeks.[15] Moreover, clinical remission between monotherapy and combination therapy was similar. In addition, a meta-analysis of RCTs showed concomitant IMs with ADL was similar to ADL monotherapy.[16] Our results are also in agreement with the recent

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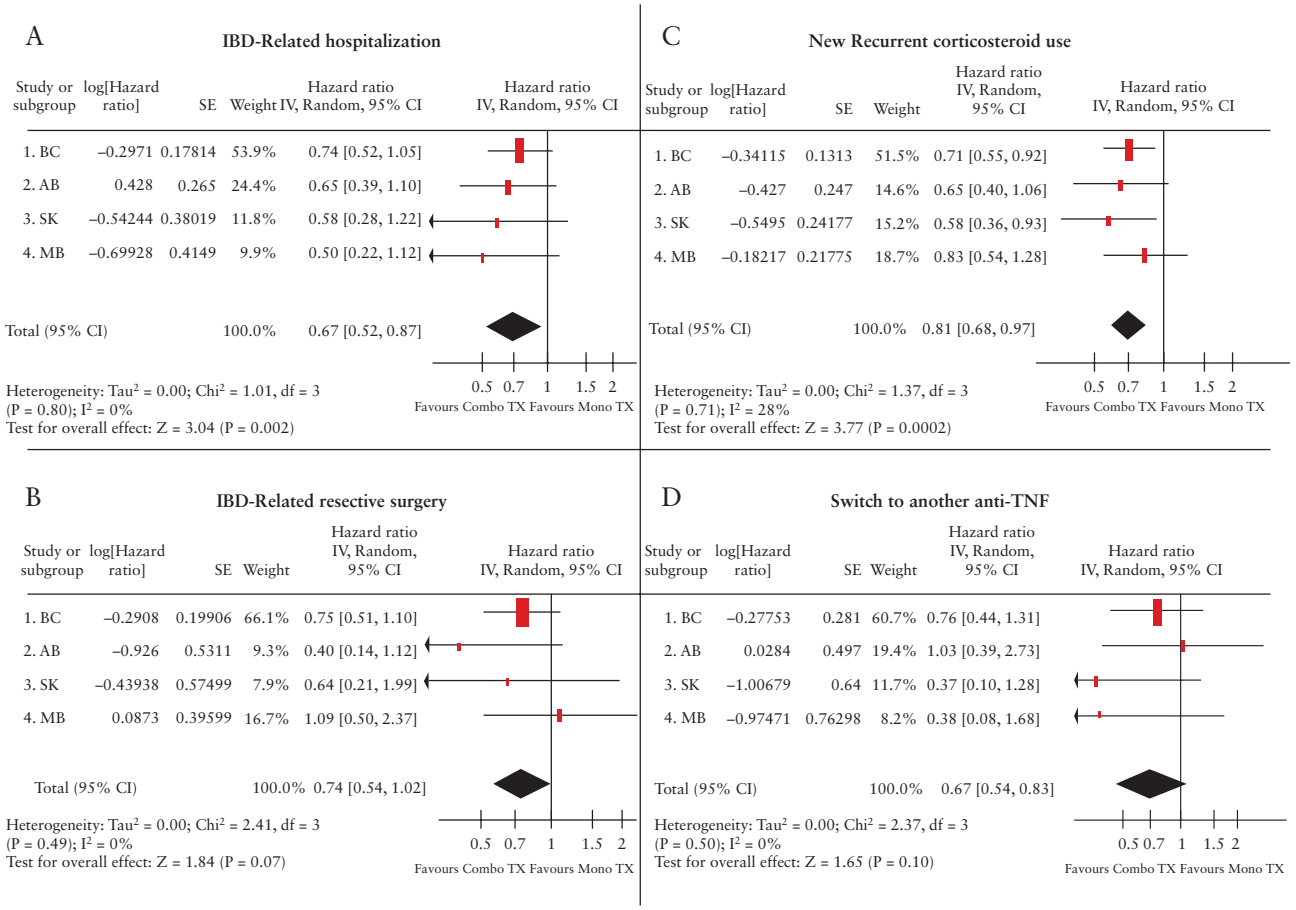

Figure 3. Association between use of combination therapy and the hazard of individual treatment failure outcomes [ulcerative colitis].

publication from the UK PANTS consortium, where combination therapy was found to be associated with a decreased odds of active disease at week 52 for patients with CD treated with IFX [aOR 0.56, 95% CI 0.38–0.83].[17] Some experts have suggested that combination therapy may not be necessary for those using ADL, as the likelihood of antibody formation is much less common with ADL than with IFX.[18,19] Although anti-TNF antibody formation is strongly associated with loss of response to therapy, the majority of patients who experience a loss of response to anti-TNF therapy do not have detectable circulating antibody levels. Combination therapy has also been shown to raise ADL trough levels,[20] which itself is associated with higher rates of clinical remission and mucosal healing.[21]

One area of potential concern is that in both CD and UC, our results suggest that the risk of treatment failure may be higher if MTX is used as the IM over a thiopurine. In both SONIC and SUCCESS-UC, the two trials which most strongly support the use of combination therapy to promote clinical remission and mucosal healing, AZA was used as the immunomodulatory agent. In recent years, there has been increasing reticence about using thiopurines either as monotherapy or as a component of combination therapy due to their side effect profile as well as numerous studies showing that thiopurine-based combination therapy is associated with an increased risk of haematological malignancies and opportunistic infections.[7–9,22] As a result, clinicians may be looking for an alternative agent to thiopurines for combination therapy.[23] MTX is effective in preventing anti-TNF-directed antibody formation and also is associated with higher circulating anti-TNF levels when compared to monotherapy in adults.[24] However, the only RCT which evaluated the role of MTX as the immunomodulatory component of combination therapy [COMMIT] was not able to demonstrate a benefit to the combination of IFX and MTX over IFX alone.[6] The use of MTX-based combination therapy was also associated with more frequent disease flares than AZA-based combination therapy in a prospectively followed French IBD cohort.[25] Moreover, there are no prospective trial data which have shown the benefits of MTX-based combination therapy in UC. Our data suggest that using MTX in place of a thiopurine to reduce the risk of rare opportunistic infections and malignancies may come at the expense of a higher rate of much more common IBD flares or loss of response, at least in UC. Siegel *et al*. used a Monte Carlo model to demonstrate that the risks of combination therapy outweigh its benefits in the very unlikely scenario that lymphoma rates are in fact 65× higher than what has previously been reported, or if the rates of opportunistic infection increase by a factor of 4.[26] Further studies to compare the rate of attaining clinical and endoscopic remission for combination therapy with thiopurines vs MTX are warranted.

Another important finding seen in this study is that in spite of high-quality evidence and numerous guidelines advocating for combination therapy over monotherapy, a majority of the individuals in this cohort did not receive a concomitant IM when starting anti-TNF therapy. We have previously demonstrated similar levels of combination therapy use in Manitoba, and moreover, we have not seen an increase in the uptake of combination therapy use in the year following the publication of SONIC in 2010.[27] Similarly, low

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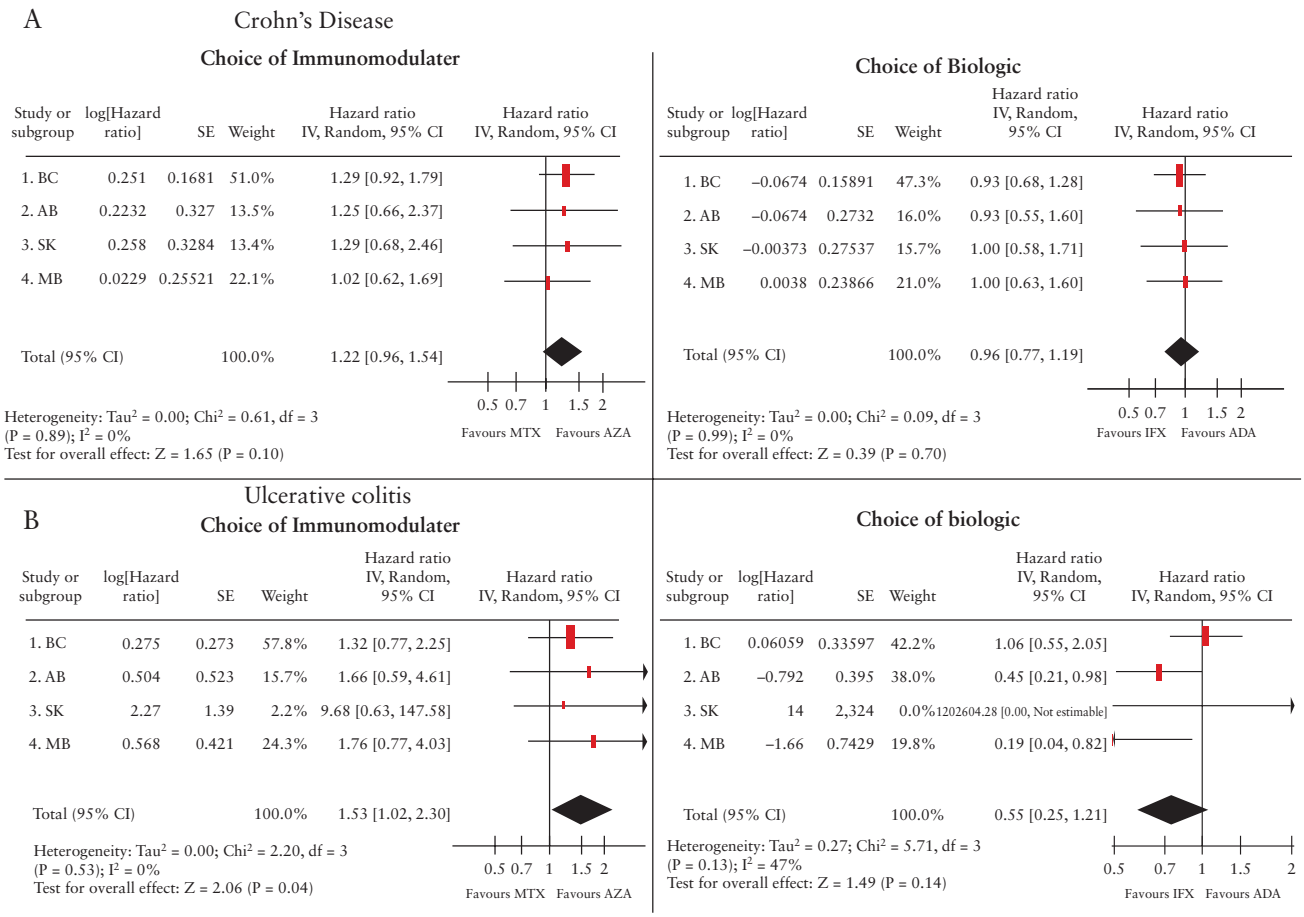

Figure 4. Effect of the choice of biologic and immunomodulator on the risk of any treatment failure among patients receiving combination therapy.

rates of combination therapy use have been seen in US and French IBD cohorts.[28,29] It is unclear whether the low use of combination therapy is driven by patient or physician factors. In our cohort, over 80% of patients had been exposed to immunomodulatory agents prior to starting anti-TNF therapy, and patients and their care providers may have been reticent to continue a class of medications that had either not been sufficiently effective or potentially led to side effects. There are also emerging data suggesting that more aggressive dosing of anti-TNF monotherapy, and/or prospectively monitoring drug levels to ensure adequate circulating anti-TNF concentrations, is associated with higher rates of clinical and endoscopic remission.[30–33] In time, this strategy may obviate the need for combination therapy, although a pragmatic trial comparing monotherapy with combination therapy guided by therapeutic drug monitoring has not yet taken place.[34] In the meantime, further study should be encouraged to identify barriers to the use of combination therapy, and to develop protocols to direct patients towards combination therapy where appropriate.

This study has some notable limitations. First, as these analyses used administrative health data and did not directly review patient charts, we were not able to detect other events which may have been indicative of a lack of an optimal response to therapy, such as worsening symptoms or increased endoscopic activity which was not severe enough to require hospitalization, surgery or the need for corticosteroids. Second, although we controlled for many potential confounders, there may be unmeasurable variables that are associated both with the patient/clinician's decision to use combination or monotherapy and the likelihood of response. These include disease characteristics that cannot be derived from administrative data, such as disease severity, extent and phenotype, or other important patient characteristics such as smoking status. We did not include fistulizing disease as a surgical outcome in the main analysis; an exploratory analysis performed using Manitoba data alone showed the rate of IBD-related surgery within 2 years of anti-TNF initiation increased from 14.5% to 15.3%. It is possible that the decision to use combination therapy over monotherapy or vice versa may be associated with other aspects of the provision of IBD care, disease course, patient adherence, performance of therapeutic drug monitoring or other unmeasured confounders that are themselves associated with improved outcomes, or that patients who agree to use combination therapy may be more likely to have other behaviours which may lead to reduced hospitalizations. Additionally, most of the outpatient physician–patient interactions are captured in the used administrative databases; however, not all of the interactions between salaried physicians and patients might in the databases given that shadow billing is not required for physicians under this specific payment method. These limitations are balanced by the important strengths of being one of the largest population-based assessments of biological therapy outcomes and the comprehensiveness of the data collection.

In summary, we have found that the use of combination therapy was associated with a 20–25% reduction in the likelihood of hospitalization, surgery, corticosteroid use and the need to switch therapy when compared to monotherapy for CD and UC. Our data also suggest that the use of MTX over AZA as the immunomodulatory

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Table 2. Baseline demographics of cohort of anti-TNF users

	BC		AB		SK		MB	
	CD	UC	CD	UC	CD	UC	CD	UC
N [overall]	2812	1270	3343	1177	1122	367	852	303
N [incident cases]	1511	919	803	385	954	300	716	262
Age at receipt of first anti-TNF								
<25.0 years	653 [23.2]	237 [18.6]	574 [17.2]	218 [5.2]	189 [16.9]	77 [21.0]	192 [22.5]	72 [23.8]
25.0–64.9 years	2013 [71.6]	944 [74.3]	2586 [77.3]	895 [76.0]	862 [76.8]	264 [71.9]	625 [73.3]	210 [69.3]
≥65.0 years	146 [5.2]	89 [7.0]	183 [5.5]	64 [5.5]	71 [6.3]	26 [7.1]	35 [4.1]	21 [6.9]
n [%] Female	1414 [50.3]	547 [43.1]	1763 [52.7]	507 [43.1]	599 [53.4]	178 [48.5]	455 [53.4]	140 [46.2]
n [%] Male	1398 [49.7]	723 [56.9]	1580 [47.3]	670 [56.9]	523 [46.6]	189 [51.5]	397 [46.6]	163 [53.8]
n [%] era of 1st anti-TNF use								
Prior to March 2005	351 [12.5]	24 [1.9]	n/a	n/a	160 [14.3]	0 [0]	123 [14.4]	12 [4.0]
Apr 2005–Mar 2009	632 [22.5]	179 [14.1]	n/a	n/a	217 [19.3]	67 [18.3]	201 [23.6]	36 [11.9]
Apr 2009–end of the study period	1829 [65.0]	1067 [84.0]	n/a	n/a	745 [66.4]	300 [81.7]	528 [63.5]	255 [84.2]
Mean disease duration prior to anti-TNF initiation, ±SD [Incident cases only]	4.00 [3.78]	3.86 [3.88]	1.20+/-0.08	1.28+/-0.13	6.33 +/- 4.89	5.02 +/- 5.10	8.7 +/- 8.2	6.0 +/- 6.3
n [%]with IBD hospitalization in year before TNF initiation	780 [27.7]	502 [39.5]	1245 [37.2]	527 [44.8]	325 [29.0]	175 [47.7]	233 [27.3]	90 [29.7]
n [%]with history of resective intestinal surgery	675 [24.0]	86 [6.8]	903 [27.0]	53 [4.5]	231 [20.6]	14 [3.8]	281 [33.0]	24 [7.9]
n [%] corticosteroid use								
In previous 90 days	1011 [36.0]	769 [60.6]	997 [29.8]	669 [56.8]	493 [43.9]	258 [70.3]	335 [39.3]	198 [65.3]
In previous 365 days	1571 [55.9]	1021 [80.4]	1570 [47.0]	872 [74.1]	711 [63.4]	325 [88.6]	482 [56.6]	254 [83.8]
Ever	2334 [83.0]	1197 [94.3]	1944 [58.2]	979 [83.2]	951 [84.8]	353 [96.2]	714 [83.8]	292 [96.4]
n [%] immunomodulator use								
In previous 90 days	1539 [54.7]	643 [50.6]	1342 [40.1]	521 [44.2]	597 [53.2]	157 [42.8]	539 [63.3]	168 [55.4]
In previous 365 days	1999 [71.1]	802 [63.1]	1901 [56.8]	664 [56.4]	763 [68.0]	201 [54.8]	663 [77.8]	218 [71.9]
Ever	2384 [84.8]	943 [74.3]	2323 [69.5]	743 [63.1]	920 [82.0]	221 [60.2]	756 [88.7]	251 [82.8]
Anti-TNF used								
IFX	1981 [70.4]	1127 [88.7]	1652 [49.4]	881 [74.9]	800 [71.3]	337 [91.8]	617 [72.4]	284 [94.3]
ADA	831 [29.6]	143 [11.3]	1691 [50.6]	296 [25.1]	322 [28.7]	30 [8.2]	235 [27.6]	17 [5.7]
N [%] using combination therapy	1233 [43.9]	556 [40.6]	1044 [31.2]	426 [36.1]	448 [40.0]	113 [30.8]	451 [52.9]	137 [45.2]
With IFX	899 [45.3%]	499 [44.3]	558 [33.8]	345 [39.2]	351 [43.9]	103 [30.5]	375 [56.8]	131 [46.1]
With ADA	334 [40.2%]	57 [39.8]	486 [28.7]	81 [29.3]	97 [29.2]	10 [33.3]	100 [42.6]	6 [35.1]
With AZA/6MP	1029 [83.4]	548 [91.1]	857 [82.1]	413 [96.9]	407 [90.8]	104 [92.0]	375 [83.1]	118 [88.7]
With MTX	204 [11.6]	54 [8.9]	187 [17.9]	13 [3.1]	41 [9.2]	9 [8.0]	76 [16.9]	15 [11.3]

6-MP, 6-mercaptopurine; ADA, adalimumab; AZA, azathioprine; IFX, infliximab; MTX, methotrexate; SD, standard deviation; TNF, tumor necrosis factor.

agent when combination therapy is used may be suboptimal in UC. Further work should be performed to determine the relative effectiveness of MTX vs AZA in combination therapy in prospective cohorts. In addition, given the low rates of combination therapy utilization in the community, programmes should be developed to encourage and support the use of combination therapy in anti-TNF users, or to confirm the use of therapeutic drug monitoring strategies that may obviate the need for combination therapy.

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Funding

This work was supported through a grant from the Crohn's and Colitis Canada Grants in Aid of Research and the Helmsley Foundation.

Conflict of Interests

L.T. has received investigator initiated funding from Janssen Canada, and served on advisory boards for AbbVie Canada, Takeda Canada, Merck Canada, Pfizer Canada and Mallinckrodt USA. C.B. has served on advisory Boards for AbbVie Canada, Ferring Canada, Janssen Canada, Shire Canada, Takeda Canada, and Pfizer Canada; Consultant for Mylan Pharmaceuticals; Educational grants from Abbvie Canada, Pfizer Canada, Shire Canada, Takeda Canada, and Janssen Canada; Speaker's panel for Abbvie Canada, Ferring Canada, Medtronic Canada, and Shire Canada; received research funding from Abbvie Canada. H.S. has been on advisory board of Pendopharm, Ferring, Takeda and Merck Canada; received educational grant from Ferring and investigator initiated research funding from Merck Canada. J.J. has been on advisory boards, acted as a consultant and been a speaker for Advisory, consultant, speaker fees for Janssen, Abbvie. G.K. has received speaking or consultancy honoraria from AbbVie, Janssen, Pfizer, Takeda and Shire; received a grant from Abbvie, Janssen, Merck, and Shire. S.M. has received honoraria for speaking or consultancy from Abbvie, Janssen, Takeda, Pfizer, Shire and Ferring. E.I.B. was supported by a New Investigator Award from the Canadian Institutes of Health Research, Crohn's and Colitis Canada, and Canadian Association of Gastroenterology; also supported by the Career Enhancement Program of the Canadian Child Health Clinician Scientist Program. M.E.K. was supported by a Post-doctoral Fellowship from the Canadian Institutes of Health Research, Crohn's and Colitis Canada, and Canadian Association of Gastroenterology.

Acknowledgments

We thank members of the Canadian Gastrointestinal Epidemiologic Consortium for their contribution to this study. Special thanks to Ms. Adebanke Oketola for her organizing and maintaining the data outputs from different provinces.

Author Contributions

Study concept and design: L.T., E.B., C.B., G.K. Acquisition of data: L.T.. Analysis and interpretation of data: L.T., E.B., C.B., H.S., S.C., M.E.K., S.M. Drafting of the manuscript: L.T. Critical revision of the manuscript for important intellectual content: L.T., E.B., C.B., H.S., A.A.Z., M.E.K., S.C., J.J., G.K., S.M., G.N., J.N.P.S. Statistical analysis: L.T., A.T. Obtained funding: L.T., E.K.

Disclaimer

This study is based in part on de-identified data provided by Alberta Health Services, Ministry of Health of British Columbia and Population Data BC, Saskatchewan Ministry of Health and eHealth Saskatchewan, and Manitoba Health. The interpretation and conclusions contained herein are those of the researchers and do not necessarily represent the views of the Government of Alberta, Government of British Columbia, Government of Saskatchewan, eHealth Saskatchewan or the Ministry of Health, or the Government of Manitoba.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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