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Sequential Combination Therapy Versus Monotherapy: A Lack of Benefit in Time to Inflammatory Bowel Disease-Related Surgery

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Abstract

Background—The benefits of combination therapy with infliximab and azathioprine have been demonstrated in clinical trials of patients with ulcerative colitis (UC) and Crohn's disease (CD). Concerns remain regarding the ideal duration and benefits of adding therapies in a sequential manner.

Aims—We aim to compare long-term outcomes among patients with inflammatory bowel disease (IBD) treated with sequentially added combination therapy or monotherapy strategies .

Methods—We performed a retrospective cohort study involving adult patients with UC and CD. One cohort included patients treated with infliximab, adalimumab, or a thiopurine as monotherapy. A second cohort included patients treated with sequentially added combination therapy including infliximab or adalimumab and a thiopurine. The primary outcome was the rate of IBD-related surgery. **Results** Among 462 patients, 181 (39 %) were treated with combination therapy. 12 % of patients treated with combination therapy underwent an IBD-related surgery compared to 18 % of patients treated with monotherapy ($p = 0.091$), with no overall difference in time to IBD-related surgery demonstrated (log-rank test, $p = 0.063$). When evaluating the subtypes of IBD, there was a significant benefit in time to IBD-related surgery among patients with CD treated with sequentially added combination therapy (HR 0.46, 95 % CI 0.25-0.85) but not UC (HR 0.82, 95 % CI 0.30-2.22).

Conclusions—The benefits of sequentially added combination therapy seem blunted when evaluating long-term clinical outcomes. This may be due to a decreased effectiveness of sequential combination therapy, a loss of benefit over time, or a differential effect between subtypes of IBD.

Keywords

Inflammatory bowel disease; Combination therapy; Infliximab; Adalimumab; Azathioprine

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Compliance with ethical standards

Conflict of interest The authors have no other financial relationships to disclose.

Introduction

While the treatment of inflammatory bowel disease (IBD) has historically relied heavily on the use of steroid therapy and immunosuppressive medications such as azathioprine (AZA), mercaptopurine (MP), and methotrexate (MTX), the introduction of biologic agents such as the anti-tumor necrosis factor (anti-TNF) agents infliximab (IFX) and adalimumab (ADA) has significantly changed the approaches to management [1–10]. When the anti-TNF agents were initially introduced, there was a tendency to utilize these agents only when the historical mainstay treatments such as immunosuppressives had failed. However, newer algorithms utilizing earlier introduction of biologic agents, and in particular combination therapy with an anti-TNF agent and an immunosuppressive medication, have demonstrated improved clinical outcomes for patients with IBD [11–16]. These demonstrated improvements in clinical outcomes have led to further questions and exploration regarding the optimal strategy for management of patients with ulcerative colitis (UC) and Crohn's disease (CD) [17, 18], with significant debate surrounding the use of anti-TNF monotherapy versus combination therapy with an immunosuppressive agent such as AZA or MP [19].

The landmark prospective trials (SONIC [11] and UC SUCCESS [13]) demonstrating the superiority of combination therapy were designed such that combination therapy with IFX and AZA was initiated concomitantly and evaluated short-term clinical outcomes (<52 weeks). In a separate examination of the long-term effects of IFX on outcomes in patients with steroid-dependent UC, combination therapy with IFX and AZA was an independent predictor of sustained clinical response [12]. However, a more recent meta-analysis has indicated that when anti-TNF therapy is added to an existing immunosuppressive regimen for patients with CD, combination therapy is no more effective than anti-TNF monotherapy in inducing clinical remission at 6 months, inducing or maintaining a response, or inducing partial fistula closure [20]. As such, it may be difficult to directly extrapolate the results of SONIC and UC SUCCESS to all patients with CD or UC, or to patients treated with combination therapy utilizing other anti-TNF therapies.

The specific aim of this study was to compare combination therapy to monotherapy as a treatment strategy when an anti-TNF agent and an immunosuppressive medication were added in sequential fashion by comparing time to IBD-related surgery over a longer duration of therapy than that used in earlier clinical trials.

Materials and Methods

Study Population

We performed a retrospective cohort study, examining data from adult patients with UC and CD treated at the Brigham and Women's Hospital Crohn's and Colitis Center between 1998 and 2014. This study was approved by the Partners Healthcare Institutional Review Board prior to inception. The medical records from the patients evaluated were all previously entered into a central electronic database. For analysis in this study, patients were included if they met all of the following criteria: (1) age ≥ 18 years, (2) a diagnosis of UC, CD, or indeterminate colitis, (3) prior documented treatment with IFX, ADA, AZA, or MP either as monotherapy or in a combination therapy regimen, (4) all data (including start and stop

dates) were available regarding the duration of combination therapy (if applicable). If any information was missing from the initial database entry, the patient's medical record was reviewed for any supplemental information that could complete their background data.

Definition of Cohorts

Patients were grouped into cohorts based on prior exposure to treatment regimens. One cohort included those patients previously treated with IFX, ADA, AZA, or MP as monotherapy. A second cohort was composed of patients previously treated at any time with combination therapy including IFX or ADA and any of the other immunosuppressive agents. The duration of monotherapy prior to the initiation of combination therapy was not factored into the analysis, and time on combination therapy was used to assess outcomes. Patients were evaluated from the initiation of monotherapy or combination therapy to the time of surgery, medication discontinuation, or the end of the study period. If a patient utilized both IFX and ADA as part of a combination therapy at separate times, both time periods of combination therapy were evaluated, with only the first occurrence of an outcome being recorded. Given concerns regarding a less substantial benefit when using MTX as the immunosuppressive medication in a combination therapy regimen [21], we chose to evaluate only combination therapy utilizing thiopurine immunosuppressive agents. If a patient was treated with monotherapy at separate time periods without an outcome event, the therapy utilized for the longest treatment period was analyzed. If a patient was currently on a therapy at the time of this study, then the stop date for their therapy was indicated as November 14, 2014, which was the date of initial review for this study.

Definition of Clinical Outcomes

The primary clinical outcome was the time to IBD-related surgery while treated with a combination or monotherapy treatment strategy, including up to 4 months after therapy was discontinued. The primary outcome was analyzed as binary “yes/no” outcomes, reporting the first IBD-related surgery during the time period, even if the patient required multiple IBD-related surgeries during this time period. Only those surgeries performed for luminal disease were counted as IBD-related surgeries, with procedures performed for perianal disease (such as seton placement) excluded from the evaluation.

In a smaller subset of patients, data were available regarding hospital admissions since 2011. As a secondary outcome, in this subset of patients we compared hospital admissions during and up to 4 months after therapy discontinuation.

Statistical Analysis

Basic descriptive characteristics for the two comparator groups are reported as raw numbers with corresponding percentages. Quantitative analysis of continuous variables including duration of therapy is reported as means with corresponding standard deviations. To evaluate our primary clinical outcome, our analysis is based on a comparison of rates of IBD-related surgery. The cumulative number of IBD-related surgery events during the evaluation period was calculated using Kaplan–Meier analysis and compared by log-rank testing. Given that multiple anti-TNF agents were used in combination therapy, we performed a sensitivity

analysis evaluating only those patients utilizing IFX as the anti-TNF in a combination therapy regimen.

Time to event (IBD-related surgery) curves were tabulated as Kaplan–Meier curves examining (1) monotherapy versus combination therapy among all patients with IBD; (2) monotherapy versus combination therapy among patients with CD; and (3) monotherapy versus combination therapy among patients with UC. Time to event curves were tabulated using time to IBD-related surgery or censoring event at the time of last recorded date of therapy utilized. An additional time to event curve was tabulated comparing monotherapy versus combination therapy among all patients with IBD within the first 6 years of therapy initiation, where any patients with an observation time greater than 312 weeks were censored at 312 weeks.

We used semiparametric Cox proportional hazards analyses to evaluate the association between type of therapy (monotherapy vs. combination therapy) and incident IBD-related surgery. We developed a series of multivari-able Cox proportional hazards models. All models were adjusted for the following list of potential confounders that were specified a priori based on clinical knowledge: age, duration of disease, and type of IBD (CD vs. UC). We also plotted the estimated time to surgery by treatment group based on the Cox model adjusting for other covariates. All statistical analyses were performed using SAS (version 9.3) statistical software (SAS Institute, Cary, NC, USA).

Results

From the original database of 629 patients from the Brigham and Women's Crohn's and Colitis Center, 462 patients met criteria for inclusion in our study. Eighty patients were excluded due to a lack of definitive data regarding the initiation date of therapy, 35 patients were excluded due to concomitant initiation of combination therapy, and 52 patients were excluded due to treatment with MTX. Of the 462 patients included in our study, 317 (69 %) patients had CD, 138 (30 %) patients had UC, and 7 (1 %) patients had indeterminate colitis. A total of 181 (39 %) patients were treated with combination therapy at some time during the study period. The disease characteristics and demographics were similar between the combination therapy and monotherapy groups, as demonstrated in Table 1; however, patients within the combination therapy group were more likely to be diagnosed at a younger age and were more likely to have UC than patients in the monotherapy group. The average duration of combination therapy was 107 weeks [standard deviation (SD) 116], which was not significantly different when compared to the overall average duration of monotherapy (101 weeks, SD 123), $p = 0.572$. There was no significant difference between duration of monotherapy with an immunosuppressive agent (96 weeks, SD 149) and monotherapy with an anti-TNF therapy (102 weeks, SD 120), $p = 0.798$.

Among those patients treated with combination therapy, 154 (85 %) utilized combination therapy with IFX as the biologic agent and 48 (27 %) utilized ADA. Twenty-one (12 %) patients received separate periods of combination therapy utilizing IFX and ADA as an anti-TNF therapy. Of the 181 patients who were treated with combination therapy, 136 (75 %) were initiated on an immunosuppressive agent prior to utilization of a combination therapy

strategy. Of these 136 patients, 82 (60 %) were initiated on MP and 54 (40 %) were initiated on AZA. A smaller portion of patients (45 total) were treated with anti-TNF therapy prior to ultimate treatment with a combination therapy regimen. Thirty-eight (84 %) patients were treated with IFX prior to initiating combination therapy, and 7 (16 %) were treated with ADA prior to initiating combination therapy. Among patients treated with a monotherapy strategy, 30 (11 %) patients were treated with a thiopurine while 251 (89 %) patients were treated with an anti-TNF therapy.

For those patients treated with an immunosuppressive agent prior to the initiation of combination therapy, the average duration of therapy with an immunosuppressive agent prior to combination therapy was 170 weeks (SD 190). The average duration of therapy with an anti-TNF therapy prior to combination therapy was 76.6 weeks (SD 107).

There was no statistically significant difference in rates of IBD-related surgery when comparing those patients treated with sequentially added combination therapy to those patients treated with monotherapy. Among patients treated with combination therapy, 22 of 181 (12 %) patients underwent an IBD-related surgery compared to 51 of 281 (18 %) patients treated with monotherapy ($p = 0.091$). When the rates of IBD-related surgery were stratified by IBD diagnosis, there was no significant difference in patients with UC ($p = 1.00$) or CD ($p = 0.142$) when comparing the two treatment strategies. When comparing only those patients treated with monotherapy, there was no significant difference between those patients treated with monotherapy with an anti-TNF agent and those patients treated with monotherapy with an immunosuppressive agent ($p = 0.084$). Although we included data from a 16-year period of time, it should be noted that 82 % of the surgeries were performed between 2009 and 2014, though there was no difference in time trends between those patients treated with sequentially added combination therapy or monotherapy ($p = 0.288$). A comparison of the types of surgeries performed in each group is shown in Table 2.

When evaluating time to IBD-related surgery, we found no significant difference when comparing the monotherapy to sequentially added combination therapy treatment strategies (for therapy-stratified long-rank tests $p = 0.063$, Table 3). Kaplan–Meier curves were stratified by type of therapy and are depicted in Fig. 1. Among patients with CD or UC, there was no significant difference in time to surgery between monotherapy and combination therapy (for therapy-stratified long-rank tests $p = 0.062$ and $p = 0.978$, respectively, Table 3). In an unadjusted Cox proportional hazards model, we observed no significant difference in time to surgery between patients on monotherapy and combination therapy (HR 0.63, 95 % CI 0.38–1.13). When adjusted for age, years since IBD diagnosis, and IBD diagnosis, we also found no significant difference in time to surgery when comparing the two therapy groups (HR 0.69, 95 % CI 0.40–1.19).

The ultimate disease course of patients with CD and UC differs, as does the utilization of surgery as a therapy in these two subtypes of IBD; thus, we performed separate Cox proportional hazards models controlling for disease-specific severity markers. In an adjusted model controlling for 3 components of the Montreal classification of disease (age, location, and behavior) we demonstrated a significant benefit in time to IBD-related surgery among patients with CD treated with sequentially added combination therapy (HR 0.46, 95 % CI

0.25–0.85). Among patients with UC there was no significant difference in time to IBD-related surgery among patients treated with sequentially added combination therapy compared to monotherapy, after controlling for Montreal classification of UC extent (HR 0.82, 95 % CI 0.30–2.22).

Given concerns regarding the heterogeneity of the combination therapy regimens that were being analyzed, we performed multiple analyses to evaluate the validity of our findings. When evaluating only patients utilizing IFX as the anti-TNF agent in a combination therapy regimen, there was no significant difference in time to surgery ($p = 0.123$). There were also concerns that the beneficial effects of sequentially added combination therapy may diminish over time; thus, we re-evaluated our outcomes by analyzing rates of IBD-related surgery within 6 years (312 weeks) of therapy initiation. In this evaluation, sequentially added combination therapy was associated with less IBD-related surgeries than monotherapy (13 vs. 18 %, $p = 0.042$, Fig. 2). However, when this subpopulation was evaluated in a Cox proportional hazards model adjusting for age, years since IBD diagnosis, and IBD diagnosis, there was no significant difference in time to IBD-related surgery when comparing the two strategies (HR 0.66, 0.38–1.1). An additional concern was that patients treated with sequentially added combination therapy might receive the second therapy too late in the disease course to influence outcomes. To analyze this concern, we evaluated all patients initiating a second therapy within 16 weeks of the first therapy in a combination therapy regimen. There were 9 patients who met these criteria; however, none of these patients went on to have an IBD-related surgery.

To evaluate a second important clinical outcome of hospital admission, we evaluated a smaller subset of 226 patients with hospitalization data obtained since 2011. In this population, 18 of 65 (28 %) patients were hospitalized while being treated with combination therapy compared to 51 of 161 (32 %) patients treated with monotherapy ($p = 0.633$). Hospitalization was evaluated as a binary outcome; however, the range of hospitalizations in the combination therapy cohort ranged from 0 to 4 and from 0 to 5 in the monotherapy cohort.

Discussion

This study demonstrated no significant difference between the use of sequentially added combination therapy utilizing an anti-TNF agent and an immunosuppressive medication and monotherapy utilizing any of these agents alone when comparing time to IBD-related surgery among patients with UC and CD. Despite an overall longer duration of combination therapy (mean 107 weeks, SD 116 weeks) for our entire study population than has been reported in prior studies [11, 13, 22], we failed to demonstrate a significant clinical benefit of combination therapy as defined by time to IBD-related surgery. When the study period was limited to the first 6 years after therapy initiation, sequentially added combination therapy was associated with less IBD-related surgeries, though there was no difference in time to IBD-related surgery after controlling for age, IBD diagnosis, and years since IBD diagnosis. Additionally, while there was no significant difference in time to IBD-related surgery among patients with CD, after controlling for severity of disease as defined by Montreal classification, sequentially added combination therapy was associated with a

significantly decreased risk of IBD-related surgery. This study represents a retrospective “real-world” analysis of sequentially added combination therapy and monotherapy as a strategy for the management of UC and CD.

Prior randomized clinical trials have demonstrated improvement in clinical outcomes in patients with both CD [11] and UC [13], when patients underwent concomitant initiation of biologic agent and immunosuppressive agent. In the SONIC trial, patients with CD were required to be anti-TNF, AZA, MP, and MTX naive prior to initiation of therapy [11]. Similarly, in the UC SUCCESS trial, patients were required to be anti-TNF naive, and a 3-month AZA-free period was required prior to enrollment, if patients were not AZA naive [13]. Our study does not address the question of concomitantly initiated combination therapy versus monotherapy in treatment naive patients, where the results of the SONIC trial and UC SUCCESS demonstrated a definitive benefit for concomitant initiation of combination therapy with IFX and AZA.

A recent meta-analysis evaluating a more heterogeneous population of patients with CD examined study participants who were on an immunosuppressive medication at the time of clinical trial enrollment, and thus remained on this immunosuppressive therapy in combination therapy with a newly initiated anti-TNF medication [20]. Each of these patients presumably represented a prior failure of immunosuppressive monotherapy, as their anti-TNF therapy was added sequentially into a combination therapy regimen. In this meta-analysis involving clinical data from 11 studies and 1601 enrolled subjects, continued use of immunosuppressive therapy in combination with anti-TNF therapy was no more effective than anti-TNF monotherapy in inducing or maintaining clinical response or remission [20].

These results were similar to an older pooled analysis including the results from 4 clinical trials evaluating IFX in both CD and UC [23]. Another recent study of patients with CD receiving Medicare benefits demonstrated that continuing immunosuppressive therapy after adding anti-TNF in combination offered no significant improvement in clinical outcomes, including rates of IBD-related surgery or hospitalization [24]. Although Armuzzi et al. [25] found that combination therapy utilizing IFX and a thiopurine in patients with UC was an independent predictor of steroid-free remission at 12 months, on subgroup analysis of those patients treated with combination therapy, the percentage of patients that were in steroid-free remission and had not undergone colectomy was significantly higher in patients who were thiopurine naive as compared to those patients in whom thiopurine therapy had previously been attempted.

One of the suggested benefits of concomitant initiation of combination therapy has been decreased immunogenicity with decreased development of antibodies to anti-TNF medications as well as higher circulating trough levels, particularly in patients being treated with IFX [26, 27]. This explanation for the decreased benefit of sequential therapy is a less likely explanation for the decreased benefits demonstrated in our population given that a minority of patients were initiated on IFX as monotherapy prior to the addition of an immunosuppressive agent to their regimen, but it is an important consideration. We did not have pharmacokinetic or pharmacodynamic testing available for the majority of the patients included in this database, and thus, we were unable to perform further analysis in this area.

Overall, given the significant benefits of combination therapy demonstrated in the trials evaluating concomitant initiation, we would still expect some degree of synergistic benefit even with the sequential addition of agents. Given the apparent initial benefits of sequentially added combination therapy within the first 6 years of initiation as well the benefits among patients with CD after controlling for severity, the possibility also remains that the blunting of the anticipated effects of combination therapy over the entire study period may be actually be driven by our study population. There is a concern that the group of patients receiving sequentially added combination therapy may have inherent disease characteristics that represent an overall more aggressive disease pattern, thus biasing our results via confounding by indication. The unequal distribution of individuals with more severe disease to the combination therapy group would potentially lead to the conclusion that sequentially added combination therapy is no more effective than monotherapy with an anti-TNF or immunosuppressive medication.

We have attempted to control for confounding by indication by evaluating available data regarding disease severity including Montreal disease classification and number of years since diagnosis; however, the lack of other real-time clinical data such as C-reactive protein, fecal calprotectin, or clinical disease indices, and the size of our sample population limit further attempts at adjustment for confounders. The small size of our sample may also be a limitation in that it could lead to concerns of an underpowered evaluation. For example, despite a lack of significance in time to IBD-related surgery among patients with CD treated with sequentially added combination therapy, there was a significant benefit of combination therapy among patients with CD when adjusting for disease severity in the Cox proportional hazards model. There may be similar characteristics of those patients with CD where combination therapy was beneficial that we were unable to analyze further due to the small sample size. Additionally, the number of surgeries among patients with UC limits the number of variables that can be included in the Cox proportional hazards model evaluating this subtype of IBD.

As this is a retrospective analysis of a database constructed from a tertiary referral Crohn's and Colitis Center, we must consider the possibility that this population is inherently different from those evaluated in prior prospective trials demonstrating the benefit of combination therapy. As Ha et al. have previously reported [28], many patients with moderate-to-severe UC and CD seen in tertiary care referral centers would not meet criteria for inclusion in many prospective randomized controlled trials of biologic therapies [28]. While the results of randomized controlled trials offer the appeal of minimizing bias and the best available evidence in terms of efficacy of potential therapies, there remains the potential that this efficacy will be blunted when applied to the population as a whole. This limitation may potentially only be overcome by further evaluation with a larger more heterogeneous database, as the likelihood of conducting a prospective clinical trial with sequential addition of combination therapy seems limited given the previously demonstrated benefits of concomitant initiation [11, 13].

Our study is a retrospective review of data that was not obtained for the purposes of this evaluation. We chose to evaluate the end points of IBD-related surgery and hospitalization, given our inability to capture more fluid yet perhaps more clinically relevant indications of

clinical response to therapy such as Harvey Bradshaw Index, Simple Clinical Colitis Activity Index, or endoscopic assessment of mucosal healing. Additionally, trends or patterns in care may have changed throughout our study period, and it is noted that the majority of the surgeries in both the combination therapy and monotherapy population were performed after 2008.

In conclusion, we have performed a retrospective cohort study comparing the use of sequentially added combination therapy utilizing anti-TNF and immunosuppressive therapy to monotherapy with IFX, ADA, AZA, or MP. We demonstrated no significant differences in the clinical outcomes of IBD-related surgery or hospital admissions during the course of a particular therapy regimen, including the 4 months following a change in therapy. Ultimately, the decision to continue an immunosuppressive medication in a combination therapy regimen should also consider patient preferences and disease-related characteristics [19]. Given the prior studies that have demonstrated a significant benefit of combination therapy when initiated concomitantly, and the potential benefit among patients with CD suggested in our analysis, the question of decreased efficacy of combination therapy when utilized in a sequential manner remains. Thus, this issue should be re-evaluated retrospectively in larger databases or potentially in prospective, randomized controlled trials.

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Fig. 1. Time to IBD-related surgery when comparing sequentially added combination therapy and monotherapy treatment strategies among patients with IBD

Fig. 2. Time to IBD-related surgery when comparing sequentially added combination therapy and monotherapy treatment strategies among patients with IBD within the first 6 years of therapy initiation

Table 1
Clinical and demographic characteristics of patients treated with monotherapy and combination therapy strategies

	Monotherapy (<i>n</i> = 281)	Combination therapy (<i>n</i> = 181)	<i>p</i> value
Age (in years)	40.9 (SD 15.2)	39.2 (SD 12.7)	0.207
Female	155 (55 %)	106 (59 %)	0.502
Smoking history			0.476
Never smoker	184 (65 %)	130 (72 %)	
Prior smoker	25 (9 %)	11 (6 %)	
Current smoker	68 (24 %)	37 (20 %)	
Unknown	4 (1 %)	3 (2 %)	
Inflammatory bowel disease diagnosis			0.047
Crohn's disease	204 (73 %)	113 (62 %)	
Ulcerative colitis	75 (27 %)	63 (35 %)	
Montreal classification: age at diagnosis of Crohn's disease	(<i>n</i> = 204)	(<i>n</i> = 113)	0.003
0–16 years old	44 (22 %)	39 (35 %)	
17–39 years old	116 (57 %)	65 (58 %)	
40 years old and over	32 (16 %)	6 (5 %)	
Montreal classification: location of Crohn's disease			0.091
Ileal disease	39 (19 %)	19 (17 %)	
Colonic disease	46 (23 %)	14 (13 %)	
Ileocolonic disease	115 (57 %)	79 (71 %)	
Isolated upper disease	1 (<1 %)	0	
Montreal classification: behavior of Crohn's disease			0.068
Non-structuring			
Non-penetrating	82 (40 %)	30 (27 %)	
Structuring	63 (31 %)	37 (33 %)	
Penetrating	56 (28 %)	40 (36 %)	
Montreal classification: presence of perianal disease			0.229
No perianal disease	117 (57 %)	55 (48 %)	
Perianal disease	80 (48 %)	56 (49 %)	
Montreal classification: extent of ulcerative colitis	(<i>n</i> = 75)	(<i>n</i> = 64)	0.444
Ulcerative proctitis	5 (7 %)	1 (2 %)	
Left-sided colitis	22 (29 %)	20 (32 %)	
Pancolitis	44 (59 %)	40 (63 %)	

^aCategorical data presented as raw data with (%)

^bContinuous data presented as means with (SD)

^cIf Montreal classification data were unknown, patients are not listed in this table

Table 2
A comparison of inflammatory bowel disease (IBD)-related surgeries in patients treated with monotherapy or combination therapy strategies

	Monotherapy (<i>n</i> = 281)	Combination therapy (<i>n</i> = 181)
Total number of IBD-related surgeries	51 (18 %)	22 (12 %)
Reason for surgery		<i>p</i> = 0.469 ^a
Medically refractory disease	29 (57 %)	14 (64 %)
Presence of a stricture	14 (27 %)	7 (32 %)
Other	8 (16 %)	1 (5 %)

^a *p* value obtained via Fisher exact test

Table 3
A comparison of time to inflammatory bowel disease (IBD)-related surgeries in patients treated with monotherapy or combination therapy strategies

	Monotherapy (<i>n</i> = 281)	Combination therapy (<i>n</i> = 181)	
Median time to IBD-related surgery among all patients (weeks, interquartile range)	44 (13–101)	60 (16–208)	<i>p</i> = 0.063 ^a
Median time to IBD-related surgery among patients with Crohn's disease (weeks, interquartile range)	49.5 (20–101)	101 (30–208)	<i>p</i> = 0.062 ^a
Median time to IBD-related surgery among patients with ulcerative colitis (weeks, interquartile range)	8 (4.5–13.5)	12 (9–16)	<i>p</i> = 0.978 ^a

^a *p* value obtained via log-rank test