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The benefit of combination therapy depends on disease phenotype and duration in Crohn's disease

Ashwin N Ananthakrishnan¹, Atsushi Sakuraba², Edward L Barnes³, Joel Pekow², Laura Raffals⁴, Millie D Long³, and Robert S Sandler⁵

¹Division of Gastroenterology, Massachusetts General Hospital and Harvard Medical School, Boston

²Inflammatory Bowel Disease Center and Division of Gastroenterology, University of Chicago, Chicago

³Division of Gastroenterology, University of North Carolina School of Medicine, Chapel Hill

⁴Division of Gastroenterology, Mayo Clinic

⁵Center for Gastrointestinal Biology and Disease, School of Medicine, University of North Carolina, Chapel Hill

Abstract

Introduction—The impact of combination therapy on disease-related morbidity in patients with established Crohn's disease (CD) or ulcerative colitis (UC) remains to be well-defined.

Aim—To examine the effect of combination therapy on disease outcomes in CD and UC

Methods—Using a multi-center prospective cohort, we classified CD and UC patients as being on monotherapy with anti-TNF or on combination with an immunomodulator. The primary outcome was a composite of new IBD-related surgery, hospitalizations, penetrating complications, need for corticosteroids or new biologic at 1 year. Multivariable regression models adjusted for potential confounders.

Results—We included 707 patients with CD (45% combination therapy) and 164 with UC (38% combination therapy). Combination therapy was not associated with reduction in the composite outcome in either CD (OR 0.87, 95% CI 0.63 – 1.22) or UC (OR 1.45, 95% CI 0.63 – 3.38). However, while no difference was noted in those with non-stricturing, non-penetrating CD, a significant reduction in the likelihood of the outcome was seen in those with stricturing or

Address for Correspondence: Ashwin N Ananthakrishnan, MD, MPH, Massachusetts General Hospital, 165 Cambridge Street, 9th Floor, Boston, MA 02114, aananthakrishnan@mgh.harvard.edu, Phone: 617-724-9953, Fax: 617-726-3080.

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Study concept and design: Ananthakrishnan

Acquisition of data: Ananthakrishnan, Sandler, Pekow, Long, Raffals

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penetrating CD (30% vs. 39%, OR 0.58, 95% CI 0.37 – 0.90). A stronger effect was also observed in those with disease duration < 5 years (OR 0.35, 95% CI 0.14 – 0.87) compared to those with a longer duration (OR 0.75, 95% CI 0.45 – 1.27). A similar reduction in occurrence of composite outcome was noted with infliximab and with other anti-TNF biologics.

Conclusion—The benefit of combination immunomodulator-biologic therapy is stronger in those with complicated Crohn’s disease, particularly early on in their disease course.

Keywords

Crohn’s disease; ulcerative colitis; combination therapy; biologics; surgery

INTRODUCTION

Inflammatory bowel diseases (IBD; Crohn’s disease (CD), ulcerative colitis (UC)) are complex immunologically mediated diseases that affect an estimated 1.6 million individuals in the United States.^{1–4} The availability of biologic therapies, namely tumor necrosis factor- α antagonists (anti-TNF) (infliximab, adalimumab, certolizumab pegol, golimumab) and anti-integrin therapies (vedolizumab, natalizumab), have significantly increased our ability to achieve clinical and endoscopic remission.^{2, 3, 5} However, loss of response to these therapies remains an important clinical challenge, in part due to immunogenicity leading to heightened clearance and reduced drug levels.^{6–12} This has led to interest in combining biologic therapy with a conventional immunomodulator to both achieve synergy and reduce immunogenicity.

This therapeutic paradigm of combination therapy received significant momentum with the publication of landmark clinical trials in CD and UC that demonstrated greater rates of clinical and endoscopic remission with a combination of infliximab and azathioprine when compared to either agent alone.^{13, 14} However, not all randomized trials have demonstrated similar benefit^{15, 16} and observational studies have also demonstrated conflicting results with some suggesting benefit¹⁷ while others found no incremental value.¹⁸ In addition to conflicting data about efficacy, widespread use of combination immunosuppression in all IBD patients is also limited by concerns about safety including risk of opportunistic infections and therapy-related malignancy.^{19–22} In addition, the heterogeneity in clinical course of both CD and UC suggests that many patients may experience a prolonged period of mild disease and not universally require aggressive-therapy up front.^{23–26} Thus, there is a need to stratify patients who may be most likely to benefit from combination therapy.

Limitations of prior studies on the topic have been small sample size, determination of treatment outcomes retrospectively, and lack of information on hard endpoints such as hospitalizations or surgeries that contribute significantly to morbidity and healthcare costs in patients with IBD. Consequently, we performed this analysis in a prospective multi-center cohort of patients with CD and UC to determine the benefit of combination therapy with an immunomodulator over anti-TNF monotherapy.

METHODS

Study Population

The data source for our study was a prospective, multicenter cohort of patients with CD and UC, the Sinai Helmsley Alliance for Research Excellence (SHARE) cohort. Details of this cohort have been described in detail in previous publications.²⁷ In brief, the cohort included patients with a diagnosis of CD, UC or IBD-unspecified (IBDU) recruited from seven referral IBD centers within the United States – Massachusetts General Hospital, University of North Carolina-Chapel Hill, Mount Sinai Hospital New York, University of Chicago, Washington University, Cedars Sinai Medical Center, and the Mayo Clinic, Rochester. Patients aged 18 years or older who met the criteria for established IBD were approached for participation.²⁸ Upon provision of informed consent, detailed characteristics of disease, current, and past medical treatments were ascertained. Patients completed an in-person, telephone, or internet-based telephone follow-up with the research coordinator every 6–12 months where information on interval medication changes, disease-related complications, hospitalizations, and surgery was obtained.

The population for this study comprised of patients with CD, UC, or IBDU who were on anti-TNF therapy at baseline alone or in conjunction with an immunomodulator (thiopurine or methotrexate) who had a prospective follow-up of one year within the cohort. To meet this definition, a follow-up assessment needed to have occurred between 320 and 410 days (365 ± 45 days) of the baseline evaluation.

Covariates and Outcomes

Detailed demographic and disease-related information was obtained at baseline including age, race, gender, smoking status, age at diagnosis and duration of disease. Disease location in CD was defined using the Montreal classification as being ileal (L1), colonic (L2), or ileocolonic (L3) while behavior was stratified as non-penetrating, non-stricturing (B1), stricturing (B2) or penetrating disease (B3) with a modifier for perianal involvement.²⁹ Presence of either B2 or B3 disease was termed complicated CD. Disease extent in UC was defined as being restricted to the rectum (E1), left-side of the colon (E2) or entire colon (E3). Assessment of medication use at baseline included current and past medications and reason for cessation of previous therapies. Prior surgical history was also noted. Our primary outcome for the study was a composite of a new IBD-related hospitalization, surgery, penetrating complication (new abscess or fistula), steroid use, or change in biologic therapy at 1 year. We analyzed each of the above outcomes separately as well.

Statistical Analysis

All statistical analysis was performed using Stata 14.0 (StataCorp, College Station, TX). Continuous variables were summarized using means and standard deviation while categorical variables were described using proportions and compared using the t-test. Univariate logistic regression was performed against the composite outcome for each disease-related covariate and demographic variable. Then, multivariable logistic regression models were constructed to calculate odds ratios (OR) and 95% confidence intervals (CI) incorporating variables significant in the univariate analysis with a p-value < 0.05 or those

that had been previously described in the literature to predict the outcomes of interest. Pre-specified stratified analysis was performed by disease duration and phenotype in both CD and UC. A two-sided p-value = 0.05 in a multivariable model indicated independent statistical significance. As allocation to monotherapy or combination therapy groups was non-random, a sensitivity analysis was performed incorporating an adjustment for a propensity score in the multivariable model. The propensity score determined the likelihood of a given patient receiving combination therapy given baseline characteristics. Such adjustment minimizes the potential bias introduced by non-random treatment group allocation.³⁰ Institutional Review Board approval for this study was obtained from each center.

RESULTS

Study Population

Our study included a total of 871 IBD patients (707 CD, 164 UC) among whom 492 (56%) were on anti-TNF monotherapy and 379 (44%) were on combination therapy with an immunomodulator (Table 1). Patients on combination therapy were similar to those on monotherapy in demographic characteristics, age at diagnosis and disease duration. Nearly four-fifths of patients in both groups had CD. There was a trend towards a larger proportion with stricturing or penetrating disease behavior in the combination therapy group, and more frequent perianal involvement without differences in prior surgery or disease location. There was no difference in extent of UC between the two groups. The most common anti-TNFs were infliximab and adalimumab in both groups and nearly two-thirds of patients in both groups were on their first biologic agent. Three-quarters of patients on combination therapy were on thiopurines (azathioprine or 6-mercaptopurine).

Crohn's disease

On follow-up at 1 year, 276 (32%) patients had an event comprising the composite outcome (22% hospitalization, 10% surgery, 9% new biologic, 6% new fistula or abscess, and 2% new steroid prescription). Table 2 presents the results of the multivariable analysis predicting the composite outcome. Male sex was associated with a lower likelihood of having the composite adverse outcome (OR 0.58, 95% CI 0.41 – 0.81) while a history of ever smoking (OR 1.49, 95% CI 1.03 – 2.15), stricturing disease (OR 1.58, 95% CI 1.01 – 2.44) and perianal involvement (OR 2.17, 95% CI 1.48 – 3.19) increased the likelihood of this outcome.

In the overall CD cohort, combination therapy with an immunomodulator was not associated with a decrease in likelihood of the composite adverse outcome (OR 0.88, 95% CI 0.63 – 1.23). However, striking differences were obtained when stratifying by disease phenotype. While there was no benefit with combination therapy in individuals with B1 disease (OR 1.45, 95% CI 0.88 – 2.40), in patients with complicated CD (B2/B3), combination therapy was associated with a significant reduction in risk of the composite adverse outcome (OR 0.60, 95% CI 0.38 – 0.93) (Table 3) (Figure 1). Analysis of individual outcomes revealed a reduction in both IBD-related hospitalizations (OR 0.51, 95% CI 0.32 – 0.82) and surgery (OR 0.58, 95% CI 0.31 – 1.09) with combination therapy in B2/B3 disease. There were too

few events for each of the other outcomes to perform robust comparisons. Stratified analysis further revealed an effect of disease duration. The reduction in adverse outcomes in patients with B2/B3 disease was more striking in those with early CD (duration < 5 years) (OR 0.40, 95% CI 0.16 – 0.96) than in those with more established disease (OR 0.75, 95% CI 0.45 – 1.27). Dichotomizing those with B2/B3 CD at disease duration of 2 years, a trend towards benefit with combination therapy was noted in both with a duration < 2 years (n=77, OR 0.45, 95% CI 0.16 – 1.26) and duration > 2 years (n=332, OR 0.67, 0.42 – 1.07), suggesting that while there is greatest magnitude of benefit in duration < 2 years, a benefit could be demonstrated up to 5 years after diagnosis.

Our findings of a reduction in adverse outcomes in B2/B3 disease were robust after adjustment for the propensity score in the multivariable model (OR 0.57, 95% CI 0.37 – 0.90). Sensitivity analysis demonstrated that the reduction (or a trend in reduction) in adverse outcomes in B2/B3 disease was noted both with infliximab (OR 0.58, 95% CI 0.27 – 1.24) and other anti-TNF agents (OR 0.55, 95% CI 0.31 – 0.98). The effect was stronger in individuals on their second or subsequent biologic (OR 0.48, 95% CI 0.24 – 0.98) compared to those who were biologic naïve (OR 0.65, 95% CI 0.36 – 1.17) though there was limited statistical power in such subgroup comparisons.

Ulcerative colitis

Table 4 presents the results of the multivariable analysis in UC. None of the variables achieved independent statistical significance in predicting the composite adverse outcome. Specifically, combination immunomodulator-anti-TNF therapy was not associated with a reduction in occurrence of the composite adverse outcome (OR 1.55, 95% CI 0.66 – 3.62). Stratifying by disease-extent, no benefit to combination therapy was observed in those with limited (E1/E2) (OR 1.06, 95% CI 0.25 – 4.57) or extensive (E3) disease (OR 2.01, 95% CI 0.66 – 6.09).

DISCUSSION

The paradigm of using combination immunomodulator-biologic therapy received substantial support with the publication of two landmark clinical trials.^{13, 14} The SONIC study in immunomodulator-naïve CD demonstrated that higher rates of clinical remission and mucosal healing were achieved with a combination of infliximab and azathioprine when compared to either therapy alone.¹³ The UC SUCCESS trial demonstrated a similar phenomenon in UC.¹⁴ However, limitations of these two trials include restriction to patients who had not previously been on immunomodulators and limited statistical power to determine potential adverse effects of dual immunosuppressive therapy. Thus, whether a benefit of combination therapy extends to real-world clinical practice of patients, many of whom had previously failed anti-TNF or immunomodulator monotherapy, is not well established and the subgroups of patients most likely to benefit have been poorly defined.

Using data from a prospective, multicenter cohort, we demonstrate that the benefit of combination therapy in CD is most striking in those with complicated stricturing or penetrating CD, particularly within 5 years of diagnosis. The latter observation is consistent with prior studies demonstrating that the greatest benefit with treatment may be early in the

disease course.³¹ In the PRECISE 2 trial of certolizumab pegol, nearly 90% of patients with disease duration less than 1 year were able to maintain response compared to only 57% of those with disease duration of 5 years or greater.³¹ Further support for the benefit of intervening early on in the disease is indirectly derived from the higher rates of response observed in trials of anti-TNF therapy in pediatric patients compared to adults with more established disease.^{32–34} The hypothesis behind the lower rates of response with long duration of disease is the development of irreversible fibrostenotic complications and permanent bowel damage that are not be amenable to modification by medical therapy.

The literature on the potential benefit of combination therapy has been inconsistent with heterogeneity in study design and conflicting observations. As in our study, many other observational cohorts and randomized controlled trials have concluded that combination therapy did not modify outcomes in an unselected group of patients with IBD, many of whom had failed immunomodulator therapy previously. Two recent clinical trials, the COMMIT study examining a combination of infliximab and methotrexate,¹⁵ and the DIAMOND study of adalimumab and azathioprine¹⁶ failed to show an improvement in clinical outcomes with combination therapy though more detailed analysis suggested higher trough levels could be obtained than with infliximab monotherapy.¹⁵ While some retrospective cohorts have noted that combination therapy prolonged persistence on therapy,¹⁷ others have failed to find a benefit. In an analysis of Medicare data, Osterman *et al.* did not find a reduction in IBD-related hospitalizations or surgery at 1 year with combination therapy when compared to monotherapy.¹⁸ As well, post-hoc analyses of clinical trials have shown either no clinical benefit over monotherapy or only a modest improvement in efficacy with combination therapy, particularly for infliximab.^{9, 35}

It is well recognized that both CD and UC are heterogeneous in their natural history.^{2, 3, 23–26, 36, 37} While many patients present with aggressive disease at presentation or go on to develop penetrating or fibrotic complications early or require surgery, many others may have a mild course, never requiring immunosuppressive therapy or surgery. One factor driving the need to stratify patients who may derive the greatest benefit from combination therapy is concerns about safety of dual immunosuppressive therapy. In a pooled analysis of data from clinical trials of adalimumab in CD, combined immunosuppressive therapy was associated with an increased risk of opportunistic infections, particularly herpes zoster.^{19, 35} The same data also described a three-fold increase in risk of both skin and systemic malignancy with combination therapy,²⁰ a finding confirming prior observations of numerically higher risk of non-Hodgkin's lymphoma with combination therapy.^{22, 38} While we were not able to examine the risks associated with combination therapy in our population, our findings suggest that the greatest benefit may be obtained in those with complicated CD. Further studies are also needed to determine if the development of such complicated phenotype can be prevented by early institution of combination therapy. Importantly, we also show that this benefit exists not only with infliximab, but also with other formulations of anti-TNF agents in contrast to prior studies in established disease have suggested benefit primarily among infliximab users.

We acknowledge several limitations of our study. First, we did not have information on duration of anti-TNF or immunomodulator use prior to enrollment in our cohort, and thus

are not able to examine if prior response to immunomodulators influences benefit when used in combination. There is conflicting data on whether prior lack of response to thiopurines determines benefit with combination therapy. Some studies have suggested that the benefit of combination therapy is greater in the thiopurine naive setting³⁹ while others have demonstrated that prior non-response to thiopurines does not influence their benefit when used in combination with a biologic⁴⁰. Jones *et al*, in a pooled analysis of randomized trials, demonstrated concomitant immunomodulator use to be associated with increased rates of clinical remission and response with infliximab therapy even in a population where the majority had previously failed thiopurine therapy⁹. We also lacked data on duration of anti-TNF use before enrollment in our cohort; however, it has been demonstrated that the annual rate of loss of response remains the same on continued anti-TNF use, and thus we do not expect this to influence to our findings^{7, 8}. We did not have serial C-reactive protein, fecal calprotectin, or endoscopic severity scores to quantify the benefit of combination therapy on those parameters in our cohort. That being said, hospitalizations and surgeries remain key endpoints in IBD, accounting for a significant fraction of the morbidity and healthcare costs associated with these diseases. We also acknowledge limited statistical power, particularly in UC where fewer patients were on anti-TNF therapy. Furthermore, we did not have sufficient participants on anti-integrin or other biologic therapy to examine if the benefit potentially extended to such treatment mechanisms.

In conclusion, we demonstrate that a combination of immunomodulator-anti TNF therapy was associated with decreased rates of hospitalization and surgery in complicated Crohn's disease, particularly within 5 years of diagnosis. Despite concern about potential risks of dual immunosuppression, given the risks of progression of disease with inadequate control of inflammation, physicians should consider starting combination therapy in order to prevent irreversible bowel damage and ensure optimal outcomes.

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Figure 1. Impact of combination therapy on Crohn's disease outcomes at 1 year, stratified by disease phenotype

Follow-up event included a new IBD-related hospitalization, surgery, change in biologic therapy, new fistula or abscess, or initiation of systemic steroids

Disease phenotype in Crohn's disease was classified as non-penetrating, non-stricturing (B1) or stricturing (B2)/penetrating (B3) disease

Table 1

Characteristics of included participants

Characteristic	Combination therapy (n=379) (%)	Monotherapy (n=492) (%)	p-value
Mean age at diagnosis (in years)	27.4 (13.0)	28.2 (13.9)	0.36
Mean disease duration (in years)	10.6 (9.7)	11.2 (10.2)	0.33
Female	58	52	0.12
White race	89	89	0.43
Ever smoking	29	29	0.88
IBD type			0.14
Crohn's disease	83	79	
Ulcerative colitis	17	21	
CD behavior			0.051*
B1	39	49	
B2	29	25	
B3	31	26	
Location			0.14
L1	17	21	
L2	17	19	
L3	66	59	
Perianal fistula	29	21	0.013*
UC Extent			0.39
E1	5	10	
E2	27	31	
E3	68	59	
Prior IBD-surgery	42	38	0.20
Type of baseline biologic			0.38
Infliximab	44	45	
Adalimumab	43	45	
Certolizumab Pegol	13	9	
Golimumab	0.5	1	
Number of prior anti-TNFs			0.24
None	61	63	
1	28	30	
2 or more	11	7	
Type of combination therapy			
Thiopurines	74	–	
Methotrexate	26	–	

All number represent percentages unless otherwise indicated.

Table 2

Multivariable analysis of predictors of a follow-up event at 1 year in Crohn's disease

Predictor	Odds ratio	95% confidence interval
Male sex	0.58	0.41 – 0.81
Ever smoking	1.49	1.03 – 2.15
Disease duration (for each year)	0.99	0.97 – 1.01
Age at diagnosis (for each year)	1.00	0.99 – 1.01
Crohn's disease behavior		
B1	Reference	
B2	1.58	1.01 – 2.44
B3	0.91	0.57 – 1.45
Location		
L1	Reference	
L2	0.74	0.42 – 1.30
L3	0.93	0.60 – 1.43
Perianal Fistula	2.17	1.48 – 3.19
Prior Surgery	0.62	0.36 – 1.07
Combination therapy	0.88	0.63 – 1.23

Follow-up event included a new IBD-related hospitalization, surgery, change in biologic therapy, new fistula or abscess, or initiation of systemic steroids

Table 3

Stratified analysis of impact of combination therapy on follow up outcomes, stratified by disease phenotype and duration

Stratifying characteristic	Odds ratio (combination therapy vs. monotherapy (reference))	95% confidence interval
Disease Behavior		
B1 (n=307)	1.45	0.88 – 2.40
B2 / B3 (n=384)	0.60	0.38 – 0.93
Disease duration		
B1 disease		
< 5 years (n=114)	1.14	0.48 – 2.71
5 or more years (n=193)	1.83	0.95 – 3.51
B2/B3 disease		
< 5 years (n=113)	0.40	0.16 – 0.96
5 or more years (n=271)	0.75	0.45 – 1.27

Table 4

Multivariable analysis of predictors of follow-up even in ulcerative colitis

Predictor	Odds ratio	95% confidence interval
Male sex	0.78	0.34 – 1.79
Ever smoking	0.68	0.25 – 1.85
Disease duration (for each year)	0.98	0.92 – 1.04
Age at diagnosis (for each year)	1.02	0.99 – 1.05
Extent		
E1	Reference	
E2	0.87	0.15 – 5.03
E3	1.13	0.22 – 5.88
Combination therapy	1.55	0.66 – 3.62