Digestive Diseases and Sciences (2019) 64:1938–1944
https://doi.org/10.1007/s10620-019-5474-4

ORIGINAL ARTICLE

Impact of Angiotensin II Signaling Blockade on Clinical Outcomes in Patients with Inflammatory Bowel Disease

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Received: 15 March 2017 / Accepted: 17 January 2019 / Published online: 6 February 2019

Abstract

Background Preclinical data demonstrate that activation of the renin–angiotensin system (RAS) contributes to mucosal inflammation, and RAS inhibition by angiotensin-converting-enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) improves colitis in animal models. Less is known regarding the effects of RAS inhibition on clinical outcomes in inflammatory bowel disease (IBD) patients.

Aim Evaluate the impact of ACEI and ARB on clinical outcomes in IBD.

Methods Rates of IBD-related hospitalizations, operations, and corticosteroid use were evaluated retrospectively in two groups. First, 111 IBD patients taking an ACEI or ARB were compared to nonusers matched 1:1 based on sex, age, diagnosis, disease location, and hypertension diagnosis. Second, outcomes in a cohort of 130 IBD patients were compared prior to and during ACEI/ARB exposure.

Results Compared to matched controls, all IBD patients together with ACEI/ARB exposure had fewer hospitalizations (OR 0.26, $p < 0.01$), operations (OR 0.08, $p = 0.02$), and corticosteroid prescriptions (OR 0.5, $p = 0.01$). Comparing outcomes before and during ACEI/ARB use, there were no differences in hospitalizations, operations, or corticosteroid use for all IBD patients together, but patients with UC had increased hospitalizations (0.08 pre- vs. 0.16 during ACEI/ARB exposure, $p = 0.03$) and decreased corticosteroid use (0.24 pre-ACEI/ARB vs. 0.12 during ACEI/ARB exposure, $p < 0.01$) during ACEI/ARB use.

Conclusions IBD patients with ACEI/ARB exposure had fewer hospitalizations, operations, and corticosteroid use compared to matched controls. No differences in outcomes were observed in individuals on ACEI/ARB therapy when compared to a period of time prior to medication exposure.

Keywords RAS inhibition · Angiotensin-converting-enzyme inhibitor · Angiotensin receptor blocker · Inflammatory bowel disease

Introduction

Angiotensin II (AT II), in addition to hormonal effects, has pro-inflammatory properties that may play a role in inflammation in patients with inflammatory bowel disease (IBD). AT II, acting through the angiotensin II type 1 receptor (AT_1R), has been shown to stimulate reactive oxygen species, activate nuclear factor kappa B (NF-κB), and increase tumor necrosis alpha (TNFα) production from macrophages [1, 2]. Furthermore, angiotensin-converting-enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) can suppress TNFα production and prevent NF-κB translocation to the nucleus [3, 4]. AT_1R inhibition has also been demonstrated to suppress expression of mucosal vascular

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addressin cell adhesion molecule 1 (MAdCAM-1), a key leukocyte adhesion molecule which facilitates homing of intestinal lymphocytes to inflamed tissue [4, 5].

Preclinical in vivo studies as well as translational data from subjects with IBD further support the role of angiotensin signaling in mucosal inflammation. Mouse and rat colitis models that are exposed to ACEI and ARB, as well as AT_1R knockout mice, have reduced colonic inflammation compared to control mice as determined by weight, histologic bowel evaluation, and cytokine levels [7–16]. Furthermore, transgenic mice that overproduce renin are also more susceptible to develop colitis [17]. In addition, mucosal levels of angiotensin I and II are higher in colonic biopsies from patients with Crohn's colitis compared to healthy controls, and mucosal angiotensin II levels have also been shown to correlate with the degree of macroscopic inflammation in patients with Crohn's colitis [6].

Despite this evidence supporting a potential therapeutic benefit from the use of ACEI and ARB in patients with IBD, there is a lack of clinical data examining their use in subjects with Crohn's disease (CD) and ulcerative colitis (UC). As such, we sought to investigate clinical outcomes in IBD patients taking an ACEI or ARB in order to test the hypothesis that ACEI and ARB exposure is associated with improved outcomes in patients with IBD.

Methods

Data Source

We performed a retrospective analysis utilizing a cohort of patients with IBD at the University of Chicago Medical Center (UCMC). All subjects included in the analysis consented under the University of Chicago IRB #15573A.

Patient Identification

Data were collected from encounters between January 1, 2010 and September 30, 2015. Patients with a minimum of 6 months of follow-up time were included. Patients taking an ACEI or ARB regardless of type or dosage were included. For patients taking an ACEI or ARB, the start date for data collection was from the first encounter after the start of the study period at UCMC if already taking an ACEI or ARB, from the start of the study period if already established at UCMC and taking an ACEI or ARB prior to the start of the study period, or from the initiation of the ACEI or ARB if treatment was initiated after their first encounter at UCMC and after the start of the study period. Clinical outcomes were recorded to the time point when the medication was stopped, the end of the study period, or the last encounter if the patient stopped following at UCMC prior to the end of the study period, whichever came first.

For control patients, data were collected from the first encounter at UCMC if after the start of the study period or from the start of the study period if already established at UCMC. Clinical outcomes were captured either at the end of the study period or the last encounter if the patient stopped following at UCMC prior to the end of the study period.

We assessed ACEI and ARB use in two groups. In group one, patients with IBD were matched to controls with IBD using a 1:1 ratio based on age $\pm$ 5 years, gender, diagnosis (CD or UC), and disease location. Patients were also matched based on a diagnosis of hypertension (HTN) to control for potential confounding.

In group two, outcomes were compared prior to the initiation of the ACEI or ARB to the time during ACEI or ARB use in the same IBD patients. A minimum of 6 months of follow-up time both in the pre-ACEI or pre-ARB treatment period and during ACEI or ARB use was necessary for inclusion. Events in both groups that occurred in the first 180 days after ACEI or ARB initiation were excluded to censor outcomes that may have occurred without sufficient time to see an impact from the ACEI or ARB.

Outcomes

Outcomes analyzed were IBD-related hospitalizations, IBD-related operations, and number of individual outpatient corticosteroid prescriptions. For group one, new biologic and new immunomodulator prescriptions were also measured. Because of variable follow-up time, outcomes were measured on a per-year basis. An IBD-related hospitalization was captured if the patient had a primary ICD-9 diagnosis code of CD (555.x) or UC (556.x), or a secondary diagnosis of CD or UC and a primary ICD-9 code of an IBD-related complication for a hospitalization. IBD-related complications included: fistula or intra-abdominal abscess (537.4, 565.1, 567.x, 569.5, 569.81, 569.83, 596.1, 619.1); stricturing disease (560.9, 569.2, 537.3); intestinal obstruction (560.x, 568.0); perianal abscess (566.x, 569.4x); gastrointestinal hemorrhage (578.1, 578.9, 569.3); hypovolemia (276.5x); electrolyte imbalance (276.1, 276.8, 275.2, 275.3); anemia (280.x, 285.1, 285.9); or malnutrition (260, 261, 262, 263.x). IBD-related operations with the following ICD-9 codes were included: laparoscopic bowel resection (17.3x); incision of small or large intestine (45.0x); isolation of intestinal segment (45.5x); excision of small or large intestine (45.6x, 45.7x, 45.8x); intestinal anastomosis (45.9x); exteriorization of intestine (46.0x, 46.1x, 46.2x); revision or closure of intestinal stoma (46.4x, 46.5x); fixation and other repair of intestine (46.6x, 46.7x); proctotomy (48.0x); excision and resection of rectum (48.4x, 48.5x, 48.6x, 48.8x, 48.9x); repair of rectum (48.7x); incision or excision of perianal

tissue or fistula (49.0x, 49.1); repair of fistula (70.x). Additionally, age, sex, gender, race, IBD-related medication exposure, smoking status, number of IBD-related surgeries that occurred prior to study period initiation, and comorbidities including hypertension (HTN), congestive heart failure (CHF), coronary artery disease (CAD), hyperlipidemia (HLD), chronic kidney disease (CKD), diabetes mellitus (DM), and Charlson index were recorded for all patients.

Statistical Analysis

Statistical analysis of differences between cases and controls was undertaken using conditional logistic regression. The clinical outcomes, calculated on a per-year basis by dividing number of hospitalizations, operations, corticosteroid prescriptions, and new biologic or immunomodulator prescriptions by the follow-up time in years, were tested in the conditional logistic regression models. To assess changes in the clinical outcomes prior to and during ACEI or ARB use, Wilcoxon signed-rank test was used. All statistical analyses were performed using Stata/SE 15.1 (StataCorp, College Station, TX), and levels of significance were set at 0.05.

Results

Characteristics of the Study Population

Group one included a total of 222 IBD patients, 111 with ACEI or ARB exposure and 111 matched IBD patients without ACEI or ARB exposure. Eighty-one percent had CD and 19% had UC (Table 1). Matched variables were mean age (59 years), gender (52% female), hypertension diagnosis, and portion of affected bowel. For CD patients, 1% had isolated ileal disease, 17% colonic disease, and 82% ileocolonic disease. For UC patients, 24% had proctitis, 38% had left-sided disease, and 38% had pancolitis. The number of prior IBD-related operations that occurred prior to the start of data collection was similar between ACEI/ARB exposed and unexposed ($p=0.28$). Among ACEI- and ARB-exposed patients, 70 (63%) took an ACEI and 41 (37%) took an ARB. The ACEI- or ARB-exposed and unexposed groups were also similar in terms of comorbidities, IBD-related medication exposure, race, and smoking status. Median follow-up time was shorter in the ACEI- and ARB-exposed group than in the control group (1117 vs. 2092 days, $p<0.01$).

Group two consisted of 130 IBD patients, 72% with CD and 28% with UC (Table 1). Mean age was 58 years. Fifty-eight (45%) were female, and 76 (58%) took an ACEI and 54 (42%) took an ARB. The majority of patients had hypertension ($n=113$, 87%), with a substantial portion of patients also having hyperlipidemia ($n=39$, 30%) and coronary artery disease ($n=19$, 15%). Of the CD patients, 5% had isolated ileal disease, 12% colonic disease, and 83% ileocolonic disease. Twenty-two percent of UC patients had proctitis, 19% had left-sided disease, 57% had pancolitis, and 3% did not have a location specified. Median follow-up time prior to ACEI/ARB initiation was 649 days and 828 days during ACEI/ARB use.

Clinical Outcomes

Utilizing the subjects in group one, we compared rates of IBD-related hospitalizations, IBD-related operations, corticosteroid use, and new prescriptions for a biologic or immunomodulator between subjects who took an ACE or ARB and matched controls (Table 2). Examining all IBD subjects in the cohort, there were fewer hospitalizations (OR 0.26, $p<0.01$), fewer operations (OR 0.08, $p=0.02$), and fewer corticosteroid prescriptions (OR 0.5, $p=0.01$) in patients with ACEI or ARB exposure compared to unexposed control patients. However, for all IBD patients together, there were no significant differences between rates of new biologic (OR 1.22, $p=0.63$) or immunomodulator use (OR 1.74, $p=0.43$) between the two groups. When considered by diagnosis, patients with Crohn's disease with ACEI or ARB exposure had fewer hospitalizations (OR 0.31, $p=0.01$), fewer operations (OR 0.09, $p=0.03$), and less corticosteroid use (OR 0.48, $p=0.01$) than control patients. As with all IBD patients combined, there were no differences between new biologic (OR 1.25, $p=0.6$) or immunomodulator prescriptions (OR 1.62, $p=0.52$) between ACEI/ARB-exposed and unexposed patients with Crohn's disease. In UC patients, there were fewer hospitalizations and operations in patients with ACEI or ARB exposure, but this analysis was limited as there were zero hospitalizations and operations in the ACEI/ARB-exposed patients. There were fewer corticosteroid prescriptions in the ACEI/ARB-exposed patients with UC, but the differences in corticosteroid use were not significant (OR 0.59, $p=0.38$). There were also no differences in new biologic (OR 0.77, $p=0.9$) or immunomodulator prescriptions (OR 2.6, $p=0.59$) in UC patients. There were two deaths in group one; one patient with ACEI/ARB died and one patient without ACEI/ARB use died.

In group two, yearly rates of IBD-related hospitalizations, IBD-related surgeries, and corticosteroid use were examined in IBD patients before and during use of an ACEI or ARB (Table 3). Examining all IBD patients together, there were no significant differences in hospitalizations (0.1/year pre-ACEI/ARB vs. 0.19/year during ACEI/ARB exposure, $p=0.66$), operations (0.05/year pre-ACEI/ARB vs. 0.07/year during ACEI/ARB exposure, $p=0.52$, and corticosteroid prescriptions (0.19/year pre-ACEI/ARB vs. 0.2/year during ACEI/ARB exposure, $p=0.53$). In patients with CD, there were no significant differences in outcomes before or during ACEI/ARB use. In patients with UC, however, there were

Table 1 Characteristics of all IBD patients in the study populations

	Group one			Group two
	ACEI/ARB exposed ($n=111$), n (%)	ACEI/ARB unexposed ($n=111$), n (%)	p value	Pre-ACEI/ARB and during ACEI/ARB ($n=130$), n (%)
Age, years (mean ± SD)[a]	59 ± 11.8	59.4 ± 12.6		57.6 ± 12.8
Gender[a]				
Female	58 (52%)			58 (45%)
Male	53 (48%)			72 (55%)
Diagnosis[a]				
Crohn's disease	90 (81%)			93 (72%)
Ulcerative colitis	21 (19%)			37 (28%)
CD site of disease[a]				
Ileal	1 (1%)			5 (5%)
Colonic	15 (17%)			11 (12%)
Ileocolonic	74 (82%)			77 (83%)
Upper	0 (0%)			0 (0%)
UC site of disease[a]				
Proctitis	5 (24%)			8 (21%)
Left-sided	8 (38%)			7 (19%)
Pancolitis	8 (38%)			21 (57%)
Unspecified	0 (%)			1 (3%)
Medication				
ACEI	70 (63%)	–		76 (58%)
ARB	41 (37%)	–		54 (42%)
Prior surgeries				
0	57 (51%)	50 (45%)	0.28	72 (55%)
1–2	39 (35%)	42 (38%)		46 (35%)
3–4	12 (11%)	14 (13%)		11 (9%)
5+	3 (3%)	5 (4%)		1 (1%)
Previous IBD medication exposure				
Aminosalicylate	52 (47%)	51 (46%)	0.77	58 (45%)
Immunomodulator	61 (55%)	59 (53%)	0.71	73 (56%)
Biologic	44 (40%)	41 (37%)	0.92	66 (51%)
Race				
White	79 (71%)	85 (76%)	Ref	107 (82%)
African American	27 (24%)	22 (20%)	0.67	14 (11%)
Other	5 (5%)	4 (4%)	0.54	9 (7%)
Comorbidities				
Hypertension	111 (100%)	111 (100%)	–	113 (87%)
Coronary artery disease	10 (9%)	13 (12%)	0.49	19 (15%)
Chronic kidney disease	4 (4%)	5 (5%)	0.74	6 (5%)
Hyperlipidemia	33 (29%)	29 (26%)	0.24	39 (30%)
Diabetes mellitus	15 (14%)	11 (10%)	0.35	22 (17%)
Congestive heart failure	3 (3%)	2 (2%)	0.66	9 (7%)
Charlson index, mean	0.92	0.72	0.35	0.85
Smoking status				
Never	58 (52%)	67 (60%)	Ref	63 (48%)
Former	40 (36%)	31 (28%)	0.19	54 (42%)
Current	13 (12%)	13 (12%)	0.76	13 (10%)
Follow-up time, median days (IQR[b])	1117 (481–1766)	2092 (1365–2098)	< 0.01	Pre: 649 (357–1145) During: 828 (536–1300)
Death	1 (1%)	1 (1%)	–	2 (1.5%)

[a]Matched variables for group one

[b]Interquartile range

Table 2 Mean outcomes for group one, in which clinical outcomes in ACEI/ARB-exposed patients were compared to matched controls without ACEI/ARB exposure

	Outcome	ACEI/ARB exposed	ACEI/ARB unexposed	OR (95% CI)	*p* value
All IBD, $n=111$ per group	Hospitalizations per year (mean)	0.1	0.3	0.26 (0.1–0.7)	0.01
	Operations per year	0.04	0.18	0.08 (0.01–0.67)	0.02
	Corticosteroids per year	0.24	0.55	0.5 (0.3–0.82)	0.01
	New biologic prescriptions per year	0.14	0.12	1.22 (0.54–2.74)	0.63
	New immunomodulator prescriptions per year	0.07	0.05	1.74 (0.45–6.8)	0.43
CD, $n=90$ per group	Hospitalizations per year	0.13	0.31	0.31 (0.12–0.79)	0.01
	Operations per year	0.04	0.16	0.09 (0.01–0.75)	0.03
	Corticosteroids per year	0.25	0.61	0.48 (0.28–0.83)	0.01
	New biologic prescriptions per year	0.16	0.14	1.25 (0.54–2.86)	0.6
	New immunomodulator prescriptions per year	0.07	0.05	1.62 (0.38–6.89)	0.52
UC, $n=21$ per group	Hospitalizations per year	0	0.28	–	–
	Operations per year	0	0.22	–	–
	Corticosteroids per year	0.16	0.32	0.59 (0.18–1.94)	0.38
	New biologic prescriptions per year	0.06	0.07	0.77 (0.01–44.2)	0.9
	New immunomodulator prescriptions per year	0.08	0.05	2.6 (0.09–84.85)	0.59

Table 3 Mean outcomes for group two, in which clinical events before and during ACEI/ARB exposure were compared in the same patients

	Outcome	Pre-ACEI/ARB exposure	During ACEI/ARB exposure	*p* value
All IBD, $n=130$	Hospitalizations per year	0.1	0.19	0.66
	Operations per year	0.05	0.07	0.52
	Corticosteroids per year	0.19	0.2	0.53
CD, $n=93$	Hospitalizations per year	0.11	0.67	0.74
	Operations per year	0.07	0.05	0.92
	Corticosteroids per year	0.18	0.23	0.89
UC, $n=37$	Hospitalizations per year	0.08	0.16	0.03
	Operations per year	0	0.12	0.17
	Corticosteroids per year	0.24	0.12	<0.01

fewer hospitalizations prior to ACEI/ARB use (0.08/year pre-ACEI/ARB vs. 0.16/year during ACEI/ARB exposure, $p=0.03$) and more corticosteroid use prior to than during ACEI/ARB use (0.24/year pre-ACEI/ARB vs. 0.12/year during ACEI/ARB exposure, $p<0.01$). There were two deaths in group two during the follow-up period.

Discussion

This study demonstrates that when comparing clinical outcomes in the same patients with IBD before and during ACEI/ARB use, ACEI and ARB use is overall associated with no differences in clinical outcomes. In a separate cohort, however, ACEI or ARB use is associated with fewer hospitalizations, operations, and corticosteroid use compared to matched IBD patients without ACEI or ARB exposure, an effect that was seen in patients with CD but not UC.

While the comparisons in the second cohort were equivocal, the analysis in group one suggests that ACEI and ARB use is correlated with improved outcomes. There is biological plausibility supporting these findings as numerous studies have shown that angiotensin II has an important role in promoting bowel inflammation, and importantly that angiotensin signaling blockade can ameliorate colitis in animal models. While there are no previous studies evaluating ACEI or ARB use in patients with IBD to our knowledge, there are a number of preclinical studies evaluating the role of AT II on inflammatory pathways. AT_1R activation in vitro and in vivo stimulates inflammatory cytokines, pro-inflammatory transcription factors, and cellular adhesion molecules, which suggests a role for targeting the angiotensin pathway to reduce inflammation in patients with IBD [2, 3].

Supporting this hypothesis are data from multiple murine colitis models in which blockade of angiotensin signaling with ACEI or ARB has consistently improved inflammation [4, 7–16]. The findings of the current study suggest that these preclinical findings may also be applicable to patients with IBD who receive medications that block angiotensin II signaling.

There is also evidence to suggest that in addition to promoting inflammation, AT II also stimulates fibrosis via activation of transforming growth factor beta (TGF-β) [18–20]. Lessons can be learned in this area from other organ systems and diseases. For instance, AT_1R is found on hepatic stellate cells, and AT II causes proliferation and increased TGF-β production in these cells [18]. In a study of hepatitis C patients, those with hypertension had increased liver fibrosis compared to patients without hypertension, and patients who received ACEI or ARB had less fibrosis than those without exposure to these medications [21]. ACEI and ARB have also emerged as anti-fibrotic therapies for their ability to reduce cardiac fibrosis and potentially for renal and pulmonary fibrosis as well [20, 22–25]. In colitis, again there are no studies evaluating their use in patients, but in a study using a rat model of colitis, losartan reduced colorectal fibrosis [26]. ACEI or ARB use may therefore inhibit or reduce fibrotic stricture formation in CD, something that was not directly evaluated in the current study, but warrants further evaluation.

The results from group two, in which outcomes were analyzed in the same IBD patient before and after starting an ACEI or ARB, may be considered more reliable as there is a lower risk of unmeasured confounders when comparing results in the same patient. However, the results from group one showed a consistent positive association between fewer adverse clinical events and ACEI or ARB use. There are several factors that may account for the discrepancy in outcomes. Although the patients in group one were matched based on multiple variables and although baseline comorbidities as well as disease activity as inferred by portion of affected bowel, prior operations, and prior IBD-related medication use were similar between the ACEI/ARB-exposed and unexposed control patients, there is the potential that other unmeasured differences between treatment groups could lead to differences in outcomes. In contrast, the smaller sample size, potential of longer disease duration on outcomes, and fewer overall outcomes in the second analysis, which compared patients prior to and on treatment with an ACEI or ARB, may have resulted in minimal differences in outcomes of patients while on treatment compared to a time period prior to treatment.

The results of this study must be interpreted in the setting of a specific patient population. The patients in this study were older and had more comorbidities than seen in IBD patients cared for in most practices. However, with the increasing prevalence and incidence of IBD, specific considerations regarding their care need to be considered as these patients age. Additionally, with the rising rates of obesity, more patients are being started on medications to manage conditions associated with metabolic syndrome at a younger age, some of which may have an unexpected impact on IBD disease activity.

This study was also limited by the low number of UC patients. In group one, no patients with ACEI or ARB exposure had any hospitalizations or operations during the examined period, and therefore, the outcomes in UC patients in the current study should be interpreted with caution. Additionally, there was an overlap in some of the patients in both groups, and therefore, any confounding effects in group one could have been also been seen in group two. Also, while the follow-up time to measure outcomes was difference between the groups, this effect was moderated by measuring outcomes as a function of total follow-up time in the study. Lastly, all ACEI and ARB medications and dosages were included. Analyzing specific medications or different doses of these medications has the potential to show a stronger association with the outcomes.

In conclusion, there is extensive preclinical data that support a role for ACEI and ARB for decreasing bowel inflammation and fibrosis, but there have been no prior studies evaluating these medications in IBD patients beyond the preclinical setting. This study found fewer hospitalizations, operations, and corticosteroid use in IBD patients with ACEI or ARB use in IBD patients compared to matched controls, but there was no improvement seen with ACEI or ARB when comparing outcomes before or during ACEI/ARB use. The clinical application of these findings, however, is limited based on the observational nature of the study. As such, larger prospective studies are needed to further elucidate the effects of these commonly used medications in patients with IBD.

Grant support National Institute of Diabetes and Digestive and Kidney Diseases, Grant Number P30 DK42086 and National Institutes of Health, Grant Number K08 DK090152 (JP).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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