ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2022 February 26; 10(6): 1754-2052

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

Contents

Thrice Monthly Volume 10 Number 6 February 26, 2022

OPINION REVIEW

MINIREVIEWS

ORIGINAL ARTICLE

Retrospective Cohort Study

Retrospective Study

Observational Study

Prospective Study

World Journal of Clinical Cases

Thrice Monthly Volume 10 Number 6 February 26, 2022

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 10 Number 6 February 26, 2022

Contents

Contents

Thrice Monthly Volume 10 Number 6 February 26, 2022

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Navdeep Singh, MBBS, MS, Assistant Professor, Division of Transplantation, Department of Surgery, The Ohio State University, Columbus, OH 43210, United States. navdeep.singh@osumc.edu

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The *WJCC* is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJCC* as 1.337; IF without journal self cites: 1.301; 5-year IF: 1.742; Journal Citation Indicator: 0.33; Ranking: 119 among 169 journals in medicine, general and internal; and Quartile category: Q3. The *WJCC*'s CiteScore for 2020 is 0.8 and Scopus CiteScore rank 2020: General Medicine is 493/793.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

PUBLICATION DATE
February 26, 2022

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2022 February 26; 10(6): 1787-1794

DOI: 10.12998/wjcc.v10.i6.1787

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Disease exacerbation is common in inflammatory bowel disease patients treated with immune checkpoint inhibitors for malignancy

Samuel J S Rubin, Tatiana Balabanis, John Gubatan, Aida Habtezion

Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Sitkin S

Received: May 28, 2021
Peer-review started: June 1, 2021
First decision: July 14, 2021
Revised: July 19, 2021
Accepted: January 11, 2022
Article in press: January 11, 2022
Published online: February 26, 2022

Samuel J S Rubin, Tatiana Balabanis, John Gubatan, Aida Habtezion, Division of Gastroenterology and Hepatology, Department of Medicine, Stanford University School of Medicine, Stanford, CA 94305, United States

Corresponding author: Samuel J S Rubin, PhD, Postdoctoral Fellow, Division of Gastroenterology and Hepatology, Department of Medicine, Stanford University School of Medicine, Alway Building, Room M211, 300 Pasteur Drive, Stanford, CA 94305, United States. yrubin@stanford.edu

Abstract

BACKGROUND

Colitis is a known potential toxicity of immune checkpoint inhibitors (ICIs). Studies evaluating the risk of disease exacerbation following ICI treatment in patients with pre-existing inflammatory bowel disease (IBD) are limited.

AIM

To assess the clinical characteristics of IBD patients treated with ICIs and determine prevalence of subsequent IBD exacerbations.

METHODS

We conducted a retrospective cohort study of all patients in the Stanford Research Repository database with pre-existing IBD who were exposed to ICIs.

RESULTS

The prevalence of IBD exacerbation following ICI was 36.8% amongst 19 patients meeting inclusion criteria. Patients with exacerbations had more gastrointestinal-related hospitalizations (4 of 7) than patients without exacerbations (0 of 12; P = 0.0090).

CONCLUSION

The prevalence of IBD exacerbations following ICI was higher than reported rates of ICI-induced colitis and diarrhea in the general population and was associated with hospitalization.

Key Words: Inflammatory bowel disease; Immune checkpoint inhibitors; Immunotherapy; Malignancy

Core Tip: Immune checkpoint inhibitor (ICI)-mediated colitis is increasingly recognized as a complication of ICI therapy. The clinical outcomes of ICI therapy on underlying inflammatory bowel disease (IBD) in patients with malignancy is poorly understood. In this retrospective cohort study of IBD patients treated with ICIs for malignancy, we demonstrate that the prevalence of IBD exacerbation following ICI therapy was higher than reported ICI-induced colitis and diarrhea in the general population. ICI use among patients with IBD who had a disease exacerbation was also associated with increased rates of hospitalization.

Citation: Rubin SJS, Balabanis T, Gubatan J, Habtezion A. Disease exacerbation is common in inflammatory bowel disease patients treated with immune checkpoint inhibitors for malignancy. *World J Clin Cases* 2022; 10(6): 1787-1794

URL: https://www.wjgnet.com/2307-8960/full/v10/i6/1787.htm

DOI: https://dx.doi.org/10.12998/wjcc.v10.i6.1787

INTRODUCTION

Immune checkpoint inhibitor (ICI) monoclonal antibodies block surface receptors on leukocytes, triggering profound immune responses. Use of ICIs for cancer treatment is increasing; the number of Food and Drug Administration-approved indications is growing, with additional ICIs in development [1]. Immune-related adverse events (irAEs) and disease exacerbations following ICIs have been documented for pre-existing inflammatory diseases and are typically managed with prompt steroids, immunomodulators, and/or tumor necrosis factor inhibitors[2,3]. Thus, clinical benefit of ICIs for malignancy in patients with certain pre-existing conditions may be limited due to serious risks.

Gastrointestinal (GI) irAEs, including diarrhea and ICI-mediated colitis (IMC), are amongst the most common ICI-associated irAEs[4]. In the general population treated with ICIs, the incidence of diarrhea was 12.1%-13.7% for anti-programmed cell death protein (PD)-1, 30.2%-35.4% for anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4), and 9.1%-10.6% for combination ICIs, while the incidence of colitis was 0.7%-1.6% for anti-PD-1, 5.7%-9.1% for anti-CTLA-4, and 13.6% for combination ICIs[1]. Use of anti-CTLA-4 ICIs is considered to increase the risk of IMC[5,6]. Recent reports suggest that the incidence of GI irAEs following ICI administration in patients with pre-existing inflammatory bowel disease (IBD) may be higher than the general population[7-9]. While these studies provided insight into IBD exacerbation rates following ICI therapy in small cohorts at a limited number of study centers, data on patient comorbidities, medications, and baseline IBD activity were lacking and might affect irAE occurrence and recognition. Understanding the prevalence, detailed clinical characteristics and outcomes of ICI-induced IBD exacerbation in broader patient populations remains an ongoing challenge. We aimed to assess the clinical characteristics of IBD patients treated with ICIs at our previously unreported center and determine IBD exacerbation prevalence in this novel population.

MATERIALS AND METHODS

We performed a retrospective cohort study of all IBD patients exposed to ICIs from 2000 through August 13, 2020 at Stanford Healthcare using the Stanford Research Repository Tool database, as approved by the Stanford Institutional Review Board. Patients were screened by International Classification of Diseases codes (K50, CD; K51, ulcerative colitis; K52, other unspecified noninfective gastroenteritis and colitis; 555, regional enteritis; 556, other ulcerative colitis) and ICI (ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, or cemiplimab). Pre-existing IBD diagnosis and subsequent ICI administration were confirmed by chart review. All subjects with these inclusion criteria were reported. Patients whose IBD diagnosis did not predate ICI were excluded. Demographics, comorbidities, medications, disease phenotypes, and clinical outcomes were collected by chart review. The primary outcome was prevalence of IBD exacerbation following ICI, as defined by new onset bloody stool, rectal bleeding, diarrhea, and/or increased bowel movements. No patients with IBD exacerbations had documented GI infections following ICI use, as determined by GI polymerase chain reaction panel, *Clostridium difficile* toxin testing, and/or stool culture. One patient with IBD exacerbation had chronic hepatitis C virus infection, and another had a postoperative wound infection. Missing data is indicated in table footnotes. No data was imputed. Statistical analyses were performed in Microsoft Excel (16.43), GraphPad Prism (8.4.3) and R (3.3.2).

Table 1 Baseline demographics and inflammatory bowel disease characteristics stratified by inflammatory bowel disease diagnosis

	Crohn's disease	Ulcerative colitis	Indeterminate IBD
	n = 4	*n* = 14	*n* = 1
Demographics			
Age at first ICI use, yr, median, IQR	63, 4	69, 12.5	60, 0
Female sex, *n* (%)	2 (50.0)	2 (14.3)	0 (0)
White race, *n* (%)	3 (75.0)	11 (78.6)	1 (100)
Black race, *n* (%)	1 (25.0)	1 (7.1)	0 (0)
Asian race, *n* (%)	0 (0)	1 (7.1)	0 (0)
Other race, *n* (%)	0 (0)	1 (7.1)	0 (0)
Non-Hispanic ethnicity, *n* (%)	4 (100)	12 (85.7)	1 (100)
Hispanic/Latino ethnicity, *n* (%)	0 (0)	2 (14.3)	0 (0)
Never smoker, *n* (%)	2 (50.0)	5 (35.7)	0 (0)
Former smoker, *n* (%)	2 (50.0)	9 (64.3)	1 (100)
Body mass index, median, IQR	21.6, 1.7	25.5, 6.1	24.1, 0
IBD characteristics			
Age at IBD onset, yr, median, IQR[1]	56, 0	39.5, 32.8	54, 0
IBD duration, yr, median, IQR[1]	7, 1	20, 29.25	6, 0
Disease location, *n* (%)	L1: 1 (25.0)	E1: 1 (7.1)	-
	L2: 1 (25.0)	E2: 4 (28.6)	-
	L3: 2 (50.0)	E3: 7 (50.0)	-
	-	Unknown: 2 (14.3)	-
Disease behavior, *n* (%)	B1: 2 (50.0)	-	-
	B2: 1 (25.0)	-	-
	B3: 0 (0)	-	-
	Unknown: 1 (25.0)	-	-
Perianal disease, *n* (%)	0 (0)	-	-
Extra-intestinal manifestations, *n* (%)	0 (0)	0 (0)	0 (0)

[1]Unknown for 2 CD and 4 UC patients because date of IBD onset was not available.
Disease location and behavior were categorized using the Montreal classification: Location (L): L1, ileal disease; L2, colonic disease; L3, ileocolonic disease; Behavior (B): B1, inflammatory phenotype; B2, obstructive/stricturing phenotype; B3, penetrating/fistulizing phenotype; Extent (E): E1, proctitis; E2, left-sided colitis; E3, extensive/pan colitis. IQR: Interquartile range; IBD: Inflammatory bowel disease; ICI: Immune checkpoint inhibitor.

Table 2 All baseline clinical characteristics stratified by prevalence of inflammatory bowel disease exacerbation

	Exacerbation	No exacerbation	*P* value[1]
	n = 7	*n* = 12	
Demographics			
Female sex, *n* (%)	0 (0)	4 (33.3)	0.2451
Age at first ICI use, yr, median, IQR	60, 12.5	66, 9.3	0.6055
White race, *n* (%)	4 (57.1)	11 (91.7)	0.1174
Black race, *n* (%)	1 (14.3)	1 (8.3)	1.0000
Asian race, *n* (%)	1 (14.3)	0 (0)	0.3684

Other race, *n* (%)	1 (14.3)	0 (0)	0.3684
Non-Hispanic ethnicity, *n* (%)	5 (71.4)	12 (100)	0.1228
Hispanic/Latino ethnicity, *n* (%)	2 (28.6)	0 (0)	0.1228
Former smoker, *n* (%)	3 (42.9)	9 (75.0)	0.3261
Body mass index, median, IQR	24.3, 1.8	25.2 (6.7)	0.9018
Co-morbidities			
Hypertension, *n* (%)	1 (14.3)	6 (50.0)	0.1733
Hyperlipidemia, *n* (%)	3 (42.9)	6 (50.0)	1.0000
Heart failure, *n* (%)	0 (0)	3 (25.0)	0.2632
Coronary artery disease, *n* (%)	0 (0)	2 (16.7)	0.5088
Chronic kidney disease, *n* (%)	0 (0)	2 (16.7)	0.5088
Diabetes mellitus, *n* (%)	2 (28.6)	1 (8.3)	0.5232
Gastroesophageal reflux disease, *n* (%)	1 (14.3)	1 (8.3)	1.0000
Asthma, *n* (%)	0 (0)	2 (16.7)	0.5088
Chronic obstructive pulmonary disease, *n* (%)	1 (14.3)	1 (8.3)	1.0000
IBD characteristics			
Crohn's disease, *n* (%)	0 (0)	4 (33.3)	0.2451
Ulcerative colitis, *n* (%)	6 (85.7)	8 (66.7)	0.6027
Indeterminate IBD, *n* (%)	1 (14.3)	0 (0)	0.3684
Age at IBD onset, yr, median, IQR[2]	47, 28.3	56, 24.5	0.9668
IBD duration, yr, median, IQR[2]	11.5, 19.75	20, 24	0.9184
History of GI surgery before ICI use, *n* (%)	2 (28.6)	5 (41.7)	0.6562
Latest known disease state before ICI use, *n* (%)	Active: 0 (0)	Active: 0 (0)	1.0000
	Inactive: 5 (71.4)	Inactive: 10 (83.3)	0.6027
	Unknown: 2 (28.6)	Unknown: 2 (16.7)	0.6027
Latest available 25 (OH) D before ICI use, ng/mL, median, IQR[3]	38.9, 11.2	29.0, 9.5	0.8857
GI medications at start of ICI use, *n* (%)			
Aminosalicylate	3 (42.9)	3 (25.0)	0.6169
Glucocorticoid	1 (14.3)	2 (16.7)	1.0000
Cholecalciferol (vitamin D3)	3 (42.9)	3 (25.0)	0.6169
Laxative (PEG, senna glycoside, docusate)	3 (42.9)	3 (25.0)	0.6169
Anti-diarrheal (diphenoxylate-atropine, loperamide)	1 (14.3)	3 (25.0)	1.0000
TNF inhibitor	0 (0)	1 (8.3)	1.0000
Mercaptopurine	1 (14.3)	0 (0)	0.3684
Other medications at start of ICI use, *n* (%)			
Oral antibiotics	0 (0)	2 (16.7)	0.5088
Proton pump inhibitor	3 (42.9)	2 (16.7)	0.3047
Famotidine	0 (0)	2 (16.7)	0.5088
Metformin	1 (14.3)	0 (0)	0.3684
Insulin secretagogue	0 (0)	1 (8.3)	1.0000
Insulin	1 (14.3)	1 (8.3)	1.0000
Benzodiazepine	2 (28.6)	4 (33.3)	1.0000

Selective serotonin reuptake inhibitors	1 (14.3)	2 (16.7)	1.0000
Diuretic	0 (0)	4 (33.3)	0.2451
ACE inhibitor or angiotensin receptor blocker	3 (42.9)	5 (41.7)	1.0000
HMA-CoA reductase inhibitor	4 (57.1)	6 (50.0)	1.0000
Anticoagulant or antiplatelet	1 (14.3)	4 (33.3)	0.6027
Nonsteroidal anti-inflammatory drug	3 (42.9)	3 (25.0)	0.6169
Donezepil	1 (14.3)	1 (8.3)	1.0000
Glucosamine	1 (14.3)	1 (8.3)	1.0000
Ondansetron	2 (28.6)	3 (25.0)	1.0000
Chemotherapeutic kinase inhibitor	1 (14.3)	0 (0)	0.3684
Cancer characteristics and management			
Primary cancer origin, *n* (%)			
Bladder	0 (0)	5 (41.7)	0.1060
Melanoma	3 (42.9)	2 (16.7)	0.3047
Lung	2 (28.6)	4 (33.3)	1.0000
GI	1 (14.3)	1 (8.3)	1.0000
Other	1 (14.3)	3 (25.0)	1.0000
Radiation therapy for cancer, *n* (%)	5 (71.4)	9 (75.0)	1.0000
Checkpoint inhibitor, *n* (%)			
Ipilimumab	2 (28.6)	1 (8.3)	0.5232
Nivolumab	2 (28.6)	2 (16.7)	0.6027
Pembrolizumab	4 (57.1)	8 (66.7)	1.0000
Atezolizumab	0 (0)	1 (8.3)	1.0000
Avelumab	0 (0)	0 (0)	1.0000
Durvalumab	0 (0)	1 (8.3)	1.0000
Cemiplimab	0 (0)	0 (0)	1.0000
Any anti-PD-1 or -PD-L1	6 (85.7)	12 (100)	0.3684
Combination anti-CTLA-4 and -PD-1/PD-L1	1 (14.3)	1 (8.3)	1.0000

[1]*P*-values from Fisher's exact test for categorical variables or Mann-Whitney *U* test for continuous variables.
[2]Unknown for 1 patient with and 5 patients without immune checkpoint inhibitor (ICI)-attributed inflammatory bowel disease (IBD) exacerbations because date of IBD onset was not available.
[3]Unknown for 3 patients with and 8 patients without ICI-attributed IBD exacerbations.
IQR: Interquartile range; IBD: Inflammatory bowel disease; ICI: Immune checkpoint inhibitor; GI: Gastrointestinal; PEG: Polyethylene glycol; ACE: Angiotensin converting enzyme; HMA-CoA: Hydroxymethylglutaryl-coenzyme A; PD-1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; CTLA-4: Cytotoxic T-lymphocyte antigen 4.

RESULTS

Nineteen patients met inclusion criteria of pre-existing IBD and subsequent ICI therapy. Four had Crohn's disease (CD), fourteen ulcerative colitis (UC), and one indeterminate IBD (Table 1). The median age of patients with CD was 63 [interquartile range (IQR), 4] and UC was 69 (IQR, 12.5). Patients were predominantly of male sex and white race. No patients had extraintestinal IBD manifestations nor pediatric onset IBD; the median age of onset was 56 (IQR, 0) for CD and 39.5 (IQR, 32.8) for UC.

All patients had controlled asymptomatic IBD when beginning ICI therapy, after which seven developed GI irAEs consistent with IBD exacerbation (Tables 2 and 3). Median length of ICI use was 12 mo (IQR, 10) and 6.5 mo (IQR, 9.3) in patients with and without exacerbations, respectively (P = 0.3685; Table 3). Median follow-up time was 435 d (IQR, 306) and 572 d (IQR, 450) from beginning ICI therapy for patients with and without exacerbations, respectively (P = 0.4824). Demographics, comorbidities, IBD characteristics (location, behavior, *etc.*), and medications were evaluated and not associated with ICI-induced IBD exacerbation (Table 2).

Table 3 Inflammatory bowel disease management and clinical outcomes following immune checkpoint inhibitor treatment stratified by prevalence of inflammatory bowel disease exacerbation

	Exacerbation	No exacerbation	*P* value[1]
	n = 7	*n* = 12	
Follow up time, d, median, IQR	435, 306	572, 450	0.4824
Length of ICI use, mo, median, IQR	12, 10	6.5, 9.3	0.3685
Reason for ICI discontinuation, *n* (%)			
Cancer remission	1 (14.3)	1 (8.3)	1.0000
Cancer non-response	0 (0)	2 (16.7)	0.5088
Side effect(s)	1 (14.3)	3 (25.0)	1.0000
Patient preference	0 (0)	1 (8.3)	1.0000
Deceased	1 (14.3)	2 (16.7)	1.0000
Unknown	0 (0)	1 (8.3)	1.0000
Not discontinued	4 (57.1)	2 (16.7)	0.1287
GI-related hospitalization, *n* (%)	4 (57.1)	0 (0)	0.0090
GI-related surgery, *n* (%)	2 (28.6)	0 (0)	0.1228
IBD medications used after ICI initiation, *n* (%)			
Aminosalicylates	4 (57.1)	4 (33.3)	0.3765
Glucocorticoids	3 (42.9)	4 (33.3)	1.0000
TNF inhibitor	2 (28.6)	1 (8.3)	0.5232
Mercaptopurine	1 (14.3)	0 (0)	0.3684
None	2 (28.6)	5 (41.7)	0.6562
Deceased, *n* (%)	1 (14.3)	4 (33.3)	0.6027

[1]*P*-values from Fisher's exact test.

IQR: Interquartile range; IBD: Inflammatory bowel disease; ICI: Immune checkpoint inhibitor; GI: Gastrointestinal; TNF: Tumor necrosis factor.

Four of seven patients with IBD exacerbations required GI-related hospitalization following ICI treatment, compared to none of 12 patients without exacerbations (57.1% *vs* 0%; $P = 0.0090$); two patients with exacerbations required GI surgery (Table 3). IBD medical therapy following ICI was not significantly different between patients with and without IBD exacerbations (Table 3). Importantly, no patients with IBD exacerbations had documented GI infections following ICI, consistent with exacerbation due to flare of underlying IBD. One patient who had an exacerbation after ICI underwent flexible sigmoidoscopy, demonstrating circumferential colitis from the anus to distal sigmoid colon, consistent with a flare of pre-existing left-sided UC.

DISCUSSION

Recent reports suggest higher incidence of GI irAEs in patients with pre-existing IBD following ICI therapy (28%-41%) compared to the general population (diarrhea: 9.1%-35.4%; colitis: 0.7%-13.6%)[1,7-9]. We observed GI irAEs consistent with IBD exacerbations in 36.8% of IBD patients treated with ICIs in a novel patient population, which parallels this emerging pattern.

Patients with IBD exacerbations experienced more GI-related hospitalizations, half accompanied by surgery. There was no association between ICI type and IBD exacerbation. Although only three patients were on antibodies directed against CTLA-4, this is consistent with another recent report[9]. We found no associations between IBD exacerbation and non-IBD medications, including proton pump inhibitors, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, antidiabetic agents, antihypertensive agents, and others analyzed (Table 2).

Our study adds to developing literature on ICIs in IBD, providing detailed data on prevalence of IBD exacerbation and outcomes in this vulnerable population. Importantly, while GI symptoms are common amongst IBD and cancer patients and could resemble GI irAEs, all patients had controlled asymptomatic IBD prior to ICI use, and no patients with subsequent IBD exacerbations had GI

infections. Another strength of our study was inclusion of additional clinical characteristics, including medications, comorbidities, race, and ethnicity, relative to previous studies. Cohort size was limited due to the single-center nature of our study and the rarity of IBD preceding ICI therapy.

CONCLUSION

In conclusion, our data highlight that relative to non-IBD patients, those with pre-existing IBD are a vulnerable population at increased risk of ICI-induced IBD flare. These findings demonstrate the importance of closely monitoring ICIs in the setting of IBD and the need for larger prospective studies to define factors associated with ICI-induced flare in IBD patients.

ARTICLE HIGHLIGHTS

Research background

Colitis and diarrhea are immune-related adverse events associated with immune checkpoint inhibitor (ICI) therapy.

Research motivation

The risk of inflammatory bowel disease (IBD) exacerbation following ICI treatment of malignancy in these patients is poorly understood.

Research objectives

We aimed to understand clinical characteristics of IBD patients treated with ICIs for malignancy and their clinical outcomes.

Research methods

We conducted a retrospective cohort study of all IBD patients treated with ICIs for malignancy and Stanford Healthcare.

Research results

The prevalence of IBD exacerbation amongst patients treated with ICI therapy for malignancy was 36.8%. Individuals with exacerbation of pre-existing IBD had more gastrointestinal-related hospitalizations.

Research conclusions

IBD exacerbation amongst patients treated with ICIs for malignancy was higher than reported rates of colitis and diarrhea in the general population treated with ICIs for malignancy.

Research perspectives

IBD patients are vulnerable to disease exacerbation when treated with ICIs for malignancy, and close monitoring should be implemented. Further studies will aim to better understand what factors modulate risk of IBD exacerbation in patients following ICI administration.

ACKNOWLEDGEMENTS

We thank Dr. Alexa R. Weingarden, MD, PhD for helpful discussions, critiques, and feedback on the study design and manuscript.

FOOTNOTES

Author contributions: Rubin SJS, Gubatan J and Habtezion A helped plan the study, interpret data, and draft the manuscript. Rubin SJS, Balabanis T, Gubatan J and Habtezion A interpreted data; Balabanis T collected data; all authors approved the final draft submitted.

Supported by the Stanford Medical Scholars Fellowship Program to Rubin SJS.

Institutional review board statement: The study is approved by the Stanford Institutional Review Board (57160).

Informed consent statement: Because of the retrospective and anonymous character of this study, the need for informed consent was waived by the institutional review board.

Conflict-of-interest statement: All authors declare no conflicts of interest.

Data sharing statement: The full data underlying this article cannot be shared publicly due to privacy of the individuals that participated in the study. The de-identified data will be shared on reasonable request to the corresponding authors.

STROBE statement: Authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

Country/Territory of origin: United States

ORCID number: Samuel J S Rubin 0000-0001-7335-3868; Tatiana Balabanis 0000-0002-9475-6989; John Gubatan 0000- 0001-6037-2883; Aida Habtezion 0000-0002-4473-006X.

S-Editor: Wang JJ
L-Editor: A
P-Editor: Wang JJ

REFERENCES

1 **Bellaguarda E**, Hanauer S. Checkpoint Inhibitor-Induced Colitis. *Am J Gastroenterol* 2020; **115**: 202-210 [PMID: 31922959 DOI: 10.14309/ajg.0000000000000497]
2 **Coureau M**, Meert AP, Berghmans T, Grigoriu B. Efficacy and Toxicity of Immune -Checkpoint Inhibitors in Patients With Preexisting Autoimmune Disorders. *Front Med (Lausanne)* 2020; **7**: 137 [PMID: 32457912 DOI: 10.3389/fmed.2020.00137]
3 **Tison A**, Quéré G, Misery L, Funck-Brentano E, Danlos FX, Routier E, Robert C, Loriot Y, Lambotte O, Bonniaud B, Scalbert C, Maanaoui S, Lesimple T, Martinez S, Marcq M, Chouaid C, Dubos C, Brunet-Possenti F, Stavris C, Chiche L, Beneton N, Mansard S, Guisier F, Doubre H, Skowron F, Aubin F, Zehou O, Roge C, Lambert M, Pham-Ledard A, Beylot-Barry M, Veillon R, Kramkimel N, Giacchero D, De Quatrebarbes J, Michel C, Auliac JB, Gonzales G, Decroisette C, Le Garff G, Carpiuc I, Vallerand H, Nowak E, Cornec D, Kostine M; Groupe de Cancérologie Cutanée, Groupe Français de Pneumo-Cancérologie, and Club Rhumatismes et Inflammations. Safety and Efficacy of Immune Checkpoint Inhibitors in Patients With Cancer and Preexisting Autoimmune Disease: A Nationwide, Multicenter Cohort Study. *Arthritis Rheumatol* 2019; **71**: 2100-2111 [PMID: 31379105 DOI: 10.1002/art.41068]
4 **Brahmer JR**, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, Chau I, Ernstoff MS, Gardner JM, Ginex P, Hallmeyer S, Holter Chakrabarty J, Leighl NB, Mammen JS, McDermott DF, Naing A, Nastoupil LJ, Phillips T, Porter LD, Puzanov I, Reichner CA, Santomasso BD, Seigel C, Spira A, Suarez-Almazor ME, Wang Y, Weber JS, Wolchok JD, Thompson JA; National Comprehensive Cancer Network. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 2018; **36**: 1714-1768 [PMID: 29442540 DOI: 10.1200/JCO.2017.77.6385]
5 **Yao J**, Li M, Zhang H, Ge Y, Weygant N, An G. Differential risks of immune-related colitis among various immune checkpoint inhibitor regimens. *Int Immunopharmacol* 2020; **87**: 106770 [PMID: 32702598 DOI: 10.1016/j.intimp.2020.106770]
6 **Johnson DB**, Sullivan RJ, Ott PA, Carlino MS, Khushalani NI, Ye F, Guminski A, Puzanov I, Lawrence DP, Buchbinder EI, Mudigonda T, Spencer K, Bender C, Lee J, Kaufman HL, Menzies AM, Hassel JC, Mehnert JM, Sosman JA, Long GV, Clark JI. Ipilimumab Therapy in Patients With Advanced Melanoma and Preexisting Autoimmune Disorders. *JAMA Oncol* 2016; **2**: 234-240 [PMID: 26633184 DOI: 10.1001/jamaoncol.2015.4368]
7 **Grover S**, Ruan AB, Srivoleti P, Giobbie-Hurder A, Braschi-Amirfarzan M, Srivastava A, Buchbinder EI, Ott PA, Kehl KL, Awad MM, Hodi FS, Rahma OE. Safety of Immune Checkpoint Inhibitors in Patients With Pre-Existing Inflammatory Bowel Disease and Microscopic Colitis. *JCO Oncol Pract* 2020; **16**: e933-e942 [PMID: 32401685 DOI: 10.1200/JOP.19.00672]
8 **Braga Neto MB**, Ramos GP, Loftus EV Jr, Faubion WA, Raffals LE. Use of Immune Checkpoint Inhibitors in Patients With Pre-established Inflammatory Bowel Diseases: Retrospective Case Series. *Clin Gastroenterol Hepatol* 2021; **19**: 1285-1287.e1 [PMID: 32565289 DOI: 10.1016/j.cgh.2020.06.031]
9 **Abu-Sbeih H**, Faleck DM, Ricciuti B, Mendelsohn RB, Naqash AR, Cohen JV, Sellers MC, Balaji A, Ben-Betzalel G, Hajir I, Zhang J, Awad MM, Leonardi GC, Johnson DB, Pinato DJ, Owen DH, Weiss SA, Lamberti G, Lythgoe MP, Manuzzi L, Arnold C, Qiao W, Naidoo J, Markel G, Powell N, Yeung SJ, Sharon E, Dougan M, Wang Y. Immune Checkpoint Inhibitor Therapy in Patients With Preexisting Inflammatory Bowel Disease. *J Clin Oncol* 2020; **38**: 576-583 [PMID: 31800340 DOI: 10.1200/JCO.19.01674]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com