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COLAR: open-label clinical study of IL-6 blockade with tocilizumab for the treatment of immune checkpoint inhibitor-induced colitis and arthritis

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ABSTRACT

Background Immune-related adverse events due to immune checkpoint inhibitors (ICIs) are not always effectively treated using glucocorticoids and it may negatively affect the antitumor efficacy of ICIs. Interventional studies of alternatives to glucocorticoids are lacking. We examined whether interleukin-6 blockade by tocilizumab reduced ICI-induced colitis and arthritis.

Patients and methods Patients with solid cancer experiencing Common Terminology Criteria for Adverse Events (CTCAE v5.0) grade >1 ICI-induced colitis/diarrhea (n=9), arthritis (n=9), or both (n=2) were recruited and treated with tocilizumab (8 mg/kg) every 4 weeks until worsening or unacceptable toxicity. Patients were not allowed to receive systemic glucocorticoids and other immunosuppressive drugs within the 14-day screening period. The primary endpoint was clinical improvement of colitis and arthritis, defined as ≥1 grade CTCAE reduction within 8 weeks. Secondary endpoints were improvements and glucocorticoid-free remission at week 24; safety; radiologic, endoscopic, and histological changes; and changes in plasma concentrations of C reactive protein, cytokines (IL-6, IL-8, and IL-17), and YKL-40.

Results Nineteen patients were available for efficacy analysis; one patient was excluded due to pancreatic insufficiency-induced diarrhea. Patients received treatment with pembrolizumab (n=10) or nivolumab (n=4) as monotherapy or ipilimumab and nivolumab (n=5) combined. Seven patients had been initially treated with glucocorticoids, and two of them also received infliximab. Ten patients continued ICI therapy during tocilizumab treatment. The primary endpoint was achieved in 15 of 19 (79%) patients. Additional one patient had ≥1 grade reduction at week 10, and another patient had stabilized symptoms. At week 24, ongoing improvement without glucocorticoids (n=12), including complete remission (n=10), was noted. Five patients had grades 3–4 treatment-related adverse events, which were manageable and reversible.

Conclusions Tocilizumab showed promising clinical efficacy and a manageable safety profile in the treatment of ICI-induced colitis and arthritis. Our findings support the feasibility of randomized trials of immune-related adverse events.

Trial registration number NCT03601611.

WHAT IS ALREADY KNOWN ON THE TOPIC

⇒ Treatment with glucocorticoids is not always effectively treating immune-related adverse events and may negatively affect the antitumor efficacy. Tocilizumab, an anti-interleukin-6 (IL-6) receptor monoclonal antibody, may interfere with the immune system to decrease immune-related toxicities. We hypothesized that tocilizumab would result in reduced immune checkpoint inhibitor (ICI)-induced colitis and arthritis.

WHAT THIS STUDY ADDS

⇒ The results of this study demonstrate that tocilizumab has promising efficacy for management of ICI-induced colitis and/or arthritis (84% clinical benefit rate) and manageable safety profile.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ Further studies are required to confirm these results and to eventually compare efficacy of tocilizumab with currently standard approaches in the treatment of ICI-induced toxicities.

BACKGROUND

Immune checkpoint inhibitors (ICIs) targeting the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and the programmed cell death protein 1 (PD-1) pathway have shown exceptional efficacy and durable responses in a wide range of solid tumors.[1 2] However, ICIs may induce potentially severe and even lethal immune-related adverse events (irAEs) involving any organ.[1 3] Conversely, several studies have

reported a favorable relationship between irAEs and antitumoral response.[4–7] Although irAEs are usually mild and manageable, ICI discontinuation and initiation of glucocorticoids for moderate to severe irAEs are indicated. Yet, if the severity of irAEs does not decrease during initial glucocorticoids, an immunosuppressive drug should be initiated.[2 3 8–10]

The impact of glucocorticoids and other immunosuppressive drugs on the antitumoral effects of ICIs remains controversial and needs to be explored further. The exact pathophysiology underlying irAEs has not been fully elucidated; however, it is considered to be linked to disturbances of the immune checkpoints that generally maintain immunologic homeostasis.[1] In addition, an increase in T cell activation and proliferation, impaired regulatory T cell survival and increased counts of 17 T-helper (Th17) cells, proinflammatory cytokines, cross-reactivity, autoantibodies, and microbiome are speculated to be involved in irAEs, such as colitis and rheumatic disorders.[2] Especially, Th17 cells that induce interleukin-17 (IL-17) production are involved in several immune diseases, including inflammatory bowel diseases, rheumatoid arthritis, and ICI-induced colitis.[2 11] Interleukin-6 (IL-6) is a proinflammatory cytokine and a major player in inflammation and cancer progression.[12–14] IL-6 stimulates the differentiation of naïve $CD4^+$ cells into Th17 cells, and the inhibition hereof may alter the Th17–regulatory T cell balance without inhibiting the Th1 $CD4^+$ T cell subtypes that support cancer cell attacks.[11 13] Tocilizumab, an IL-6 receptor monoclonal antibody, has been approved for the management of rheumatic diseases (including rheumatoid arthritis, giant cell arteritis, systemic sclerosis), chimeric antigen receptor T cell therapy (CAR T) related cytokine release syndrome (CRS), and COVID-19.[15–18] In addition, a threefold increase of IL-17 and IL-6 parallel with the incidence of fulminant colitis has been reported in a patient with presumed ipilimumab-induced colitis.[19] Importantly, tocilizumab has been effective in managing severe CRS without compromising the antitumoral efficacy.[20] Clinical improvement in various irAEs has been observed after administration of tocilizumab in case series.[21–24] These observations of blocking IL-6 and whereby reducing IL-17, made the authors hypothesize if patients with ICI-induced colitis and arthritis could benefit from treatment with tocilizumab without using glucocorticoids. The purpose of this clinical trial was to assess the efficacy and safety of tocilizumab for treating ICI-induced colitis/diarrhea and arthritis/arthralgia, some of the most frequently occurring irAEs in patients with cancer treated with ICIs.[9 25 26]

METHODS

Study design

This investigator-initiated, single-arm, signal-seeking study enrolled patients from January 24, 2019 to February 19, 2020 at the Copenhagen University Hospital (Herlev and Gentofte, Denmark). Patients received tocilizumab (8 mg/kg, maximum dose: 800 mg) every 4 weeks for at least two cycles or until worsening or lack of improvement of ICI-induced colitis/diarrhea and arthritis, unacceptable toxicity, withdrawal of consent, clear clinical deterioration, or according to the investigator's judgment. In case of lack of reduction or worsening symptoms, tocilizumab was discontinued, and glucocorticoids were initiated according to local guidelines. Continued treatment with ICIs was allowed if deemed safe according to the investigator's judgment. Reintroduction of tocilizumab was offered to patients who had reduced colitis/diarrhea or arthritis but experienced worsening within 6 months after the last infusion. The initial stage with the efficacy assessment in seven patients, performed in June 2019, was followed by an expansion phase with an additional 13 patients (online supplemental figure S1). The study adhered to the Consolidated Standards of Reporting Trials reporting guideline (online supplemental table S1). Written informed consent was obtained from all patients.

Patient population

Patients aged ≥18 years with solid tumors were eligible if they had new-onset, glucocorticoid-refractory and/or glucocorticoid-dependent colitis/diarrhea or arthritis per Common Terminology Criteria for Adverse Events (CTCAE V.5.0) grade >1 induced by ICIs: Colitis was classified from grade 1, asymptomatic to grade 4, life-threatening, urgent intervention indicated; and diarrhea as grade 1, increase <4 stools/day over baseline to grade 4, life-threatening. Arthritis was graded as grade 1, mild pain with inflammation, erythema, or joint swelling to grade 3, severe pain associated with signs of inflammation, erythema, or joint swelling, irreversible joint damage, limiting self-care activities of daily living.[27] The grading of ICI-induced colitis/diarrhea and arthritis was conducted at the time point for starting tocilizumab. To diminish any disturbances, exposure to systemic glucocorticoids and other immunosuppressive drugs was not allowed within a 14-day screening period.

Assessments

Oncologists evaluated all patients with assistance from gastroenterologists or rheumatologists for the assessment of colitis/diarrhea and arthritis. Gastrointestinal assessment was scheduled at tocilizumab initiation and repeated after 1 month, including the following: history, physical examination, fecal analysis (pathogenic viral and bacterial species including *Clostridioides difficile* and calprotectin), and computed tomography (CT) or combined positron emission tomography CT scans. All patients with colitis/diarrhea underwent colonoscopy with biopsies at treatment initiation, including: histopathology, physicians' global assessment, and a colitis activity score (Mayo Score, online supplemental methods). Colonoscopies were repeated after 1–3 months. Rheumatological evaluation included history, physical examination,

Table 1 Characteristics of patients with colitis treated with tocilizumab

Baseline patient characteristics (colitis)						Characteristics of the patients' colitis treated with tocilizumab												
Patient ID	**Sex, Age**	**Cancer, stage Treatment (doses)**	**BOR**	**ICI-status**	**Other IrAEs than colitis (CTCAE)**	**Duration≥1 CTCAE grade before inclusion**	**Shifted from GCs**	**CTCAE grade, week 0**			**CTCAE grade, week 8**			**CTCAE grade, week 24**			**Supportive, "as needed"**	**Systemic GCs within 24 weeks**	**Response to TCZ**
								Colitis	**Diarrhea**	**Abdominal pain**	**Colitis**	**Diarrhea**	**Abdominal pain**	**Colitis**	**Diarrhea**	**Abdominal pain**			
C1	M 70y	CCA, IV Ipi 1 mg/kg+Nivo 3 mg/kg (3+1)	SD	Ongoing	None	New-onset, 4 days	No	2	3	2	↓1	↓1	↑3[A]	NE	NE	NE	Loperamide	Yes, in Week 20, due to transition to palliative care	Yes
C2	M 67y	NSCLC, IV Pembro 2 mg/kg (15)	PR	Interrupted	Rash (1)	New-onset, 3 days	No	2	1	0	NE	NE	NE	NE	NE	NE	Loperamide	Yes, shifted to prednisolone on Day 12 due to worsening	No
C9	M 66y	Melanoma, III Nivo 480 mg, adj. (2)	NE	Interrupted	None	New-onset, 33 days	No	2	3	1	↓↓0	↓1	↓↓0	↓↓0	↓↓0	↓↓0	Loperamide	No	Yes
C14	F 55y	Melanoma, IV Nivo 6 mg/kg[B] (1)	NE	Permanently discontinued	Hypothyroidism (2)	Chronic, 101 days[‡]	Yes, steroid-refractory	2	2	1	↓1	↓1	↓↓0	↓↓0	↓↓0	↓↓0	Loperamide	No	Yes
C15	M 63y	RCC, IV Ipi1mg/kg+ nivo 3 mg/kg (2)	NE	Restarted	Arthralgia (1)	New-onset, 16 days	No	2	2	1	↓1	↓1	↓↓0	NE	NE	NE	None	Yes, relapse of colitis during ICI reintroduction	Yes
C17	F 56y	CCA, IV Ipi 1mg/kg +nivo 3mg/kg (4)	SD	Interrupted	Hyperthyroidism (1), rash (1)	New-onset, 17 days	No	1	3	0	↔1	↓2	0	NE	NE	NE	Psyllium	Yes, switch to budesonide with response	No
C18	M 55y	Melanoma, IV Ipi 3 mg/kg+nivo 1 mg/kg (2)	NE	Interrupted	None	New-onset, 26 days	No	1	2	0	↓↓0	↓1	0	NE	NE	NE	Loperamide	Yes, single dose methylprednisolone due to a treatment-related reaction	Yes
C19	F 71y	Bladder cancer, IV Pembro 2 mg/kg (23)	NE	Interrupted	None	Chronic, 97 days	No	2	1	1	↓1	↓↓0	↓↓0	↓↓0	0	0	Loperamide, Psyllium	No	Yes
AC12	M 72y	NSCLC, IV Pembro 2 mg/kg (33)	PR	Permanently discontinued	Rash (1)	Chronic, 333 days[‡]	Yes, steroid-dependent	1	1	0	↓↓0	↓↓0	0	↓↓0	↓↓0	0	Loperamide	No	Yes
AC20	F 60y	Ocular melanoma, IV Pembro 2 mg/kg[B] (10)	SD	Restarted	Hypophysitis (2), pneumonitis (2)	Chronic, 787 days[‡]	Yes, steroid-dependent	2	1	1	↓1	↓0	↔1	↓↓0	↓↓0	↓↓0	Loperamide	No	Yes

The arrows indicate the following: ↔, stable/no change; ↑ or ↓, increase or decrease of CTCAE grade ≥1; and ↓↓complete remission of symptoms. Some patients were not evaluable owing to initiation of non-ICI therapy or treatment with systemic glucocorticoids for colitis or arthritis. Definition of new-onset irAEs, debut of irAEs within <90 days; chronic irAEs, debut for more than ≥90 days ago. Colitis was classified as grade 1, asymptomatic; grade 2, abdominal pain, mucus or blood in stool; grade 3, severe abdominal pain, peritoneal signs; grade 4, life-threatening, urgent intervention is indicated. Diarrhea as grade 1, increase <4 stools/day over baseline; grade 2, increase 4–6 stools/day over baseline; increase ≥7 stools/day over baseline, hospitalization indicated; grade 4, life-threatening. Abdominal pain as grade 1 mild pain; grade 2, moderate pain, limiting instrumental activities of daily living; grade 3, severe pain-limiting self-care activities of daily living.
*Cancer-related pain, requiring increased doses of morphine.
†Previous treatment with ipilimumab (3 mg/kg) plus nivolumab (1 mg/kg).
‡Management of irAE prior to screening: C14 received prednisolone 5-100 mg (192 days for colitis) and infliximab (5 mg/kg, 2 doses for colitis, last dose 45 days prior to inclusion). AC12 received prednisolone 10-23 (922 days for colitis). AC20 received prednisolone 2.5-250 mg (680 days for colitis), hydrocortisone 30 mg (62 days for hypophysitis), betamethasone IA (for artritis), infliximab (2 doses for colitis, given 2 years prior to inclusion). All others received no treatment for irAE.
AC, arthritis and colitis; BOR, best overall response; C, colitis; CCA, cholangiocarcinoma; CTCAE, Common Terminology Criteria for Adverse Events; F, female; GCs, glucocorticoids; IA, intra-articular; ICIs, immune checkpoint inhibitors; Ipi, ipilimumab; irAE, immune-related adverse events; M, male; NE, not evaluable; Nivo, nivolumab; NSCLC, non-small cell lung cancer; Pembro, pembrolizumab; PR, partial response; RCC, renal cell carcinoma; SD, stable disease; TCZ, tocilizumab.

Table 2 Characteristics of patients with arthritis treated with tocilizumab

Baseline patient characteristics (arthritis)						Characteristics of the patients' arthritis treated with tocilizumab												
Patient ID	**Sex, Age**	**Cancer, stage Treatment (doses)**	**BOR**	**ICI-status**	**Other IrAEs than arthritis (CTCAE)**	**Duration≥1 CTCAE grade before inclusion**	**Shifted from GCs**	**CTCAE grade, week 0**			**CTCAE grade, week 8**			**CTCAE grade, week 24**			**Supportive, "as needed"**	**Systemic GCs within 24 weeks**	**Response to TCZ**
								Arthralgia	**Arthritis**	**Myalgia**	**Arthralgia**	**Arthritis**	**Myalgia**	**Arthralgia**	**Arthritis**	**Myalgia**			
A3	M 76 years	NSCLC, IV Pembro 2 mg/kg (15)	SD	Ongoing	None	New-onset, 3 days	No	3	3	2	↑NE	↑NE	NE	NE	NE	NE	Arthrocentesis, GCs and lidocaine IA in both knees, 2 times in Week 1–3, paracetamol, tramadol	Yes. Worsening of arthritis during ICIs on Day 24, started prednisolone	No
A4	M 77 years	Cutaneous SCC, IV Pembro 2 mg/kg (9)	CR	Permanently discontinued	Colitis (1), hypothyroidism (2)	Chronic, 90 days†	No	2	2	2	↔2	↔2	↔2	↓↓0	0	↓↓0	Paracetamol, ibuprofen	No	Yes
A5	M 62 years	NSCLC, III Ipi1mg/kg+Nivo 3 mg/kg (4+10)	SD	Ongoing	None	New-onset, 12 days	No	3	3	0	↓↓0	↓↓0	0	↓↓0	↓↓0	0	Ibuprofen, local intra-articular injection in one knee between in week 3	Yes. ICI-induced hypophysitis	Yes
A6	F 60 years	NSCLC, IV Pembro 2 mg/kg (26)	SD	Ongoing	Psoriasis (2)	New-onset, 12 days†	No	2	2	0	↓↓0	↓1	0	↓↓0	↓↓0	0	Paracetamol, tramadol	No	Yes
A7	F 67 years	NSCLC, IV Pembro 2 mg/kg (12)	PR	Ongoing	Hypothyroidism (2), rash (1)	Chronic, 12 days†	No	2	2	1	↓↓0	↓1	↓↓0	↓↓0	↓↓0	↓↓0	Paracetamol	No	Yes
A10	F 62 years	NSCLC, III Pembro 2 mg/kg (10)	PR	Ongoing	Hepatitis (1)	New-onset, 15 days	No	2	2	0	↓1	↓1	0	↓↓0	↓↓0	0	GCs IA in both knees in Week 2, paracetamol	No	Yes
A11	F 30 years	Melanoma, III Nivo 480 mg, adj (3)	NE	Ongoing	None	New-onset, 71 days†	Yes	2	2	1	↓↓0	↓↓0	↓↓0	0	0	↔1	Diclofenac, tramadol	Yes. ICI-induced hypophysitis and non-specific irAEs	Yes
A13	F 65 years	Melanoma, IV Pembro 2 mg/kg (28)	PR	Permanently discontinued	None	Chronic, 752 days†	Yes, steroid-dependent	2	2	1	↓1	0	↔1	↓1	0	↔1	Stopped regular GCs IA	No	Yes
A16	M 55 years	Melanoma, IV Nivo 480 mg (33)	CR	Ongoing	Diarrhea (1)	New-onset, 85 days†	No	2	2	0	↓1	0	0	NE	NE	NE	Paracetamol	Yes. Switch to prednisolone due to colds and risk factors for COVID-19	Yes
AC12	M 72 years	NSCLC, IV Pembro 2 mg/kg (33)	PR	Permanently discontinued	Rash (1)	Chronic, 922 days†	Yes, steroid-dependent	2	2	1	↓1	↓1	1	↓1	↓1	1	None	No	Yes
AC20	F 60 years	Ocular melanoma, IV Pembro 2 mg/kg*	SD	Restarted	Hypophysitis (2), pneumonitis (2)	Chronic, 506 days†	Yes, steroid-dependent	2	2	0	↔2	↔2	0	↓1	0	0	Continued regular arthrocentesis and GCs IA to Week 9, stopped due to response to toci. Paracetamol, ibuprofen, and tramadol	No	Yes

The arrows indicate the following: ↔, stable/no change; ↑ or ↓, increase or decrease of CTCAE grade ≥1; and ↓↓complete remission of symptoms. Some patients were not evaluable owing to initiation of non-ICI therapy or treatment with systemic glucocorticoids for colitis or arthritis. Definition of new-onset irAEs, debut of irAEs within <90 days; chronic irAEs, debut for more than ≥90 days ago. Arthritis was graded as grade 1, mild pain with inflammation, erythema, or joint swelling; grade 2, moderate pain associated with signs of inflammation, erythema, or joint swelling limiting instrumental activities of daily living; grade 3, severe pain associated with signs of inflammation, erythema, or joint swelling, irreversible joint damage, limiting self-care activities of daily living. Arthralgia and myalgia are graded from 1 to 3 on CTCAE V.5.0 (grade 1, mild pain; grade 2, moderate pain, limiting instrumental activities of daily living; grade 3, severe pain-limiting self-care activities of daily living).

*Previous treatment with ipilimumab (3 mg/kg) plus nivolumab (1 mg/kg).

†Management of irAE prior to screening: A4 received prednisolone 25 mg for diarrhea and levothyroxine for hypothyroidism. A6 received topical GCs for psoriasis. A7 received topical GCs for rash and levothyroxine for hypothyroidism. A11 received prednisolone 25 mg (12 days) for arthritis. A13 received prednisolone 3.75-25 mg (710 days) and regular methylprednisolone IA (bimonthly) for arthritis. A16 received prednisolone 5-25 mg for diarrhea. AC12 received prednisolone 10-25 mg (922 days) for arthritis. AC20 received prednisolone 2.5-250 mg (680 days for arthritis), hydrocortisone 30 mg (62 days for hypophysitis), betamethasone IA for arthritis, infliximab (2 doses, given 2 years prior to inclusion for colitis). All others received no treatment for irAE.

AC, arthritis and colitis; BOR, best overall response; C, colitis; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; F, female; GCs, glucocorticoids; IA, intra-articular; ICIs, immune checkpoint inhibitors; Ipi, ipilimumab; irAE, immune-related adverse events; M, male; NE, not evaluable; Nivo, nivolumab; NSCLC, non-small cell lung cancer; Pembro, pembrolizumab; PR, partial response; SCC, squamous cell carcinoma; SD, stable disease; TCZ, tocilizumab.

Table 3 Radiologic, endoscopic, and histological features in patients with ICI-induced colitis

	Treatment assessment					Evaluation assessment					
Patient ID	Radiologic findings	Endoscopic findings	Physicians global assessment	Total mayo score	Histologic	Radiologic findings	Endoscopic findings	Physicians global assessment	Total mayo score	Histologic	Response to TCZ
C1	Bowel wall thickening (ascending, transverse, descending colon, and sigmoid)	Normal findings	Mild	4	Severe intraepithelial lymphocytosis; mild cryptitis, apoptosis, moderate chronic inflammation in lamina propria; increased subepithelial collagenous band	Unchanged in ascending and transverse colon, slightly increased in the descending colon and sigmoid	Mild irritation	Mild	3	Mild intraepithelial lymphocytosis ↓;mild cryptitis, apoptosis, mild chronic inflammation in lamina propria ↓; normal subepithelial collagenous band ↓	Yes
C2	Bowel wall thickening (rectum)	Edema, redness, pus, erosions from coecum to anal	Severe	10	Ulcerations; diffuse cryptitis and crypt abscesses; severe acute and chronic inflammation in lamina propria; crypt destructions; altered crypt architecture	Reduced bowel wall thickening (rectum)	Decreased redness and edema (rectosigmoid junction and rectum)	Mild	2	No ulcerations; focal cryptitis and crypt abscesses↓; mild acute and chronic inflammation in lamina propria ↓; altered crypt architecture ↔	No, glucocorticoids indicated before evaluation
C9	Bowel wall thickening (pancolitis)	Edema and minor blood extractions,	Mild	4	Cryptitis, crypt abscesses; intraepithelial lymphocytosis; apoptosis; increased amount of plasma cells and eosinophils in lamina propria	No signs of inflammation	Entire colon with edema and vulnerable mucosa	Mild	2	No cryptitis↓; no crypt abscesses; no intraepithelial lymphocytosis %; apoptosis ↔; increased amount of plasma cells and eosinophils in lamina propria ↔	Yes
AC12	NE	Normal	Normal	1	Edema; intraepithelial lymphocytosis; increased amount of plasma cells and eosinophils in lamina propria	NE	Normal	Normal	0	No edema; focal intraepithelial lymphocytosis ↓; mild chronic inflammation in lamina propria ↓	Yes*
C14	Bowel wall thickening (pancolitis)	Edema (general)	Mild	4	Erosions; cryptitis, crypt abscesses; apoptosis; moderate chronic inflammation with eosinophilia in lamina propria	No signs of colitis	Normal	Normal	0	No erosions; no cryptitis or crypt abscesses; no apoptosis; mild chronic inflammation in lamina propria ↓	Yes*
C15	Bowel wall thickening (rectosigmoid colon)	Edema rectosigmoid colon	Moderate	6	Ulceration; cryptitis, crypt abscesses; moderate chronic inflammation with eosinophilia in lamina propria	Reduced bowel wall thickening (rectum)	Normal	Mild	3	No ulceration; no cryptitis or crypt abscesses; mild chronic inflammation with eosinophilia in lamina propria↓	Yes†, but experienced relapse during ICIs. Control after initiation of glucocorticoids
C17	Bowell wall thickening (pyloric partly gastric ventricle, duodenum, jejunum, and rectum)	Normal	Normal	3	Intraepithelial lymphocytosis; chronic inflammation in lamina propria	Increased wall thickening (pyloric part of the gastric ventricle, small intestine, and rectum)	Normal	Normal	3	Normal mucosa; no intraepithelial lymphocytosis; no inflammation	No, stable symptoms. Control during budesonide

Continued

Table 3 Continued

Patient ID	Treatment assessment				Evaluation assessment					Response to TCZ
	Radiologic findings	Endoscopic findings	Physicians global assessment	Total mayo score	Histologic	Radiologic findings	Endoscopic findings	Physicians global assessment	Total mayo score	Histologic	
C18	Bowel wall thickening (ascending colon, sigmoid, and rectum)	Normal	Normal	2	Edema; mild eosinophil inflammation	Reduced stranding and bowel wall thickening (ascending colon, sigmoid, and rectum)	Normal	Normal	1	Normal mucosa; no edema; no inflammation	Yes, single dose methylprednisolone due to a treatment-related reaction
C19	Bowel wall thickening (sigmoid and descending colon)	Normal	Mild	4	Severe intraepithelial lymphocytosis; cryptitis; apoptosis; severe eosinophil inflammation in lamina propria	Reduced bowel wall thickening (descending colon)	Diffuse hyperemia (colon and rectum)	Mild	2	Mild intraepithelial lymphocytosis ↓; cryptitis ↔; apoptosis ↔; mild eosinophil inflammation in lamina propria ↓	Yes*
AC20	No signs of colitis	Edema in the left side of the colon	Mild	3	Edema; apoptosis; moderate eosinophil inflammation	No signs of colitis	Normal	Normal	0	No edema; no apoptosis; no inflammation	Yes

The arrows indicate the following: ↔, stable/no change; ↑increased, and ↓decrease.
*A second evaluation with colonoscopy was performed during follow-up and revealed ongoing endoscopic and histologic remission of colitis.
†Endoscopy was performed during glucocorticoid therapy.
A, arthritis; AC, arthritis and colitis; C, colitis; ICI, immune checkpoint inhibitors; NE, Not evaluable; TCZ, Tocilizumab.

and measurement of circulating levels of autoantibodies (antinuclear antibodies, rheumatoid factor, and anticyclic citrullinated peptide antibodies). Imaging tests were performed if indicated. We examined the patients twice in week 1, followed by every 2–3 weeks according to the investigator's judgment and irAE severity. Patients were followed up for at least 30 days (±5 days) for CTCAE assessment and then every 8–12 weeks for 6 months after the last tocilizumab dose. Plasma concentrations of C reactive protein (CRP) as part of routine analyses, cytokines (IL-6, IL-8, and IL-17), and YKL-40 were measured before initiation and every 2–3 weeks until the end of the treatment (online supplemental methods).

Outcomes

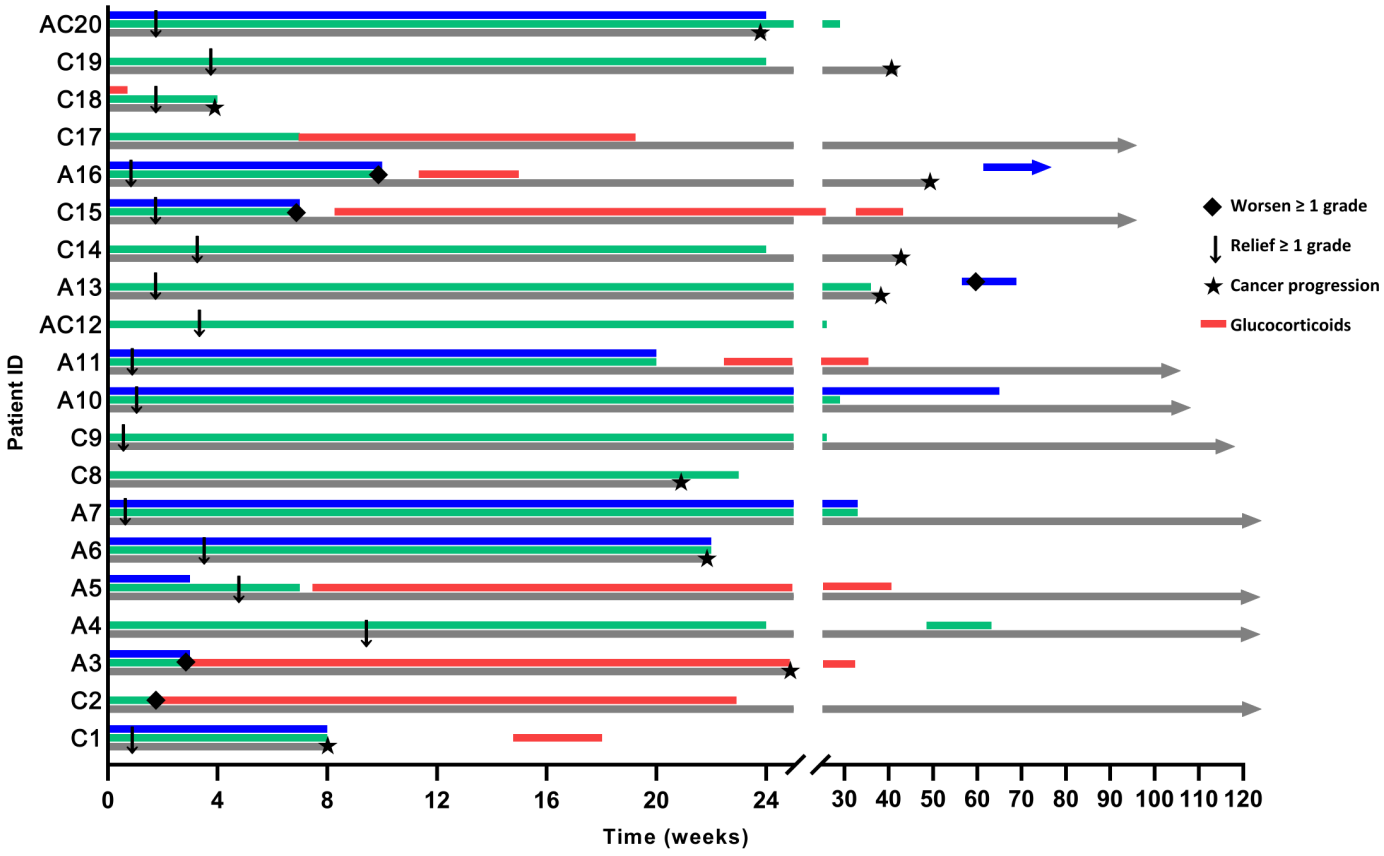
The primary endpoint was clinical benefit, defined as ≥1 grade reduction of ICI-induced colitis/diarrhea and/or arthritis using CTCAE V.5.0 within 8 weeks after tocilizumab initiation. The secondary endpoints were safety, ≥1 grade reduction without glucocorticoids within 8 weeks of treatment initiation, and sustained glucocorticoid-free remission at week 24. The exploratory endpoints were radiologic, endoscopic, and histological changes and changes in plasma concentrations of CRP, cytokines (IL-6, IL-8, and IL-17), and YKL-40 during tocilizumab.

Statistical analysis

A sample size of 20 was required according to Simon's 2-stage optimal design to obtain a significance level of 5% and a power of 80% in the one-sided test of the null hypothesis (<50% clinical benefit rate) against the alternative hypothesis (≥80% clinical benefit rate). In the first stage, seven patients were treated, and in the case of ≤4 patients with reduction of symptoms, accrual would be terminated. Otherwise, the trial would include an additional 13 patients in the second stage. The null hypothesis would be rejected if ≥14 of 20 patients with clinical benefit were observed.

All patients with ICI-induced colitis/arthritis who met the inclusion criteria and received ≥1 cycle of tocilizumab were analyzed for treatment efficacy (evaluable populations). Time to symptom reduction was defined as the time from treatment initiation (tocilizumab) to the date of ≥1 CTCAE grade reduction of symptom. Complete remission of symptoms was defined as the time from tocilizumab initiation to CTCAE grade 0 of colitis/diarrhea and arthritis.

Descriptive statistics were used to summarize the characteristics of the cohort and to report adverse events (AEs). Continuous outcome measures were presented as medians and ranges. CIs were estimated by using binomial tests. Statistical analyses were performed by using Microsoft Excel v2002 and R Studio V.1.2.5001.



	C1	C2	A3	A4	A5	A6	A7	C8	C9	A10	A11	AC12	A13	C14	C15	A16	C17	C18	C19	AC20
Duration of ICI	8	NE	3	NE	3	22	33	NE	NE	65	20	NE	NE	NE	7	10	NE	NE	NE	24
Duration of TCZ	8	2	3	24	7	22	33	23	26	72	20	26	36	24	7	10	7	4	24	29
PFS	8	141	25	133	131	22	125	21	115	104	103	PD	39	44	92	51	92	4	42	24

Figure 1 Treatment overview. All 20 patients are illustrated. Patient C8 was excluded from efficacy analysis due to pancreatic insufficiency-induced diarrhea. Treatment for ICIs and tocilizumab are shown from the time point of tocilizumab initiation. Nine of 20 patients received systematic therapy with systemic glucocorticoids. Six patients experienced cancer progression within the study period (24 weeks), including C18 with melanoma, who had new melanoma moles which were surgically resected and followed by a durable complete response. At the cut-off for disease status in October 2021, three additional patients experienced cancer progression; two were rechallenged with a PD-1 inhibitor. ICI, immune checkpoint inhibitor; NE, not evaluable; PD, progressive disease; PFS, progression-free survival; TCZ, tocilizumab.

RESULTS

Patient characteristics

Of 27 patients screened, 20 patients with arthritis (n=9), colitis/diarrhea (n=9), or both (n=2) induced by ICIs were enrolled. Seven patients were excluded: four declined to participate, two did not meet the inclusion criteria (non-ICI-related arthralgia), and one patient failed the glucocorticoid tapering. One patient with diarrhea was subsequently excluded from the efficacy analysis due to diarrhea caused by pancreatic insufficiency with no relation to ICIs (online supplemental figure S2). None had a history of autoimmune diseases. Before initiating tocilizumab treatment, the median duration of colitis/diarrhea and arthritis symptoms was 26 days (3–787) and 71 days (3–922). Seven patients had initially received systemic glucocorticoids for colitis and/or arthritis, and two of them also received treatment with infliximab for colitis (tables 1 and 2). All patients stopped receiving glucocorticoid therapy or other immunosuppressive drugs within the 14-day screening period; however, those with hypophysitis continued regular hydrocortisone substitution.

Eight of 10 patients with confirmed ICI-induced colitis/diarrhea had CT-verified bowel wall thickening; five (50%) had endoscopic changes with edema of either the entire colon or left colonic segments. The median Mayo Score was 4 (1–10). All 10 patients had biopsy-proven colitis in the absence of enteritis. Fecal calprotectin levels available in five patients ranged from 109 to >1800 µg/mg. Five of the 11 patients with arthritis were positive for antinuclear antibodies, and two for a low-level rheumatoid factor.

Efficacy outcomes

At week 8, 15 of 19 patients (79%, 95% CI 54% to 94%) had ≥1 grade reduction of symptoms without using glucocorticoids. The median time from tocilizumab initiation to reduction was 14 days for both colitis (3–28)

Table 4 Safety table

	Safety population (n=20)	
	Any grade	Grade 3–4
	N (%)	N (%)
Any AE	20 (100)	8 (40)
TRAE	16 (80)	5 (25)
Neutrophil count decreased	4 (20)	2 (10)
Platelet count decreased	4 (20)	1 (5)
Alanine transaminase increased	4 (20)	0
Aspartate transaminase increased	4 (20)	0
Anorexia	2 (10)	0
Fatigue	2 (10)	0
Cold symptoms	2 (10)	0
Colitis	1 (5)	1 (5)
Infusion-related reaction	1 (5)	1 (5)
Septic shock	1 (5)	1 (5)
Abdominal pain	1 (5)	0
Dry eyes	1 (5)	0
Dry mouth	1 (5)	0
Eczema	1 (5)	0
Headache	1 (5)	0
Hoarseness	1 (5)	0
Nausea	1 (5)	0
Pruritus	1 (5)	0
Rhinitis	1 (5)	0
Urinary tract infection	1 (5)	0
Vomiting	1 (5)	0

AE, adverse event; TRAE, treatment-related AE.

and arthritis (5–72). One of the two patients with stable symptoms who continued treatment responded at week 10. Two patients experienced worsening symptoms after a single infusion and started glucocorticoids after 12 and 24 days, respectively. All six patients with persistent colitis or arthritis (duration of ≥90 days) responded to tocilizumab treatment.

Within 24 weeks, 16 of 19 patients (84%, 95% CI 60% to 96%) achieved ≥1 grade reduction following treatment with tocilizumab. At week 24, 12 patients had ongoing reduction of symptoms, 10 of which achieved durable complete remission of symptoms; however, one patient received glucocorticoids due to other irAEs. In total, 9 of the 19 (47%) patients received systemic glucocorticoids (tables 1 and 2).

In patients with colitis, 8 of 10 (80%) patients showed a reduction in symptoms (table 1). Furthermore, patients with suspicion of cytomegalovirus (CMV) were tested negative. One patient with initial symptom reduction experienced relapse of colitis after restarting ICI therapy before evaluation and was treated with glucocorticoids. Another patient discontinued tocilizumab due to treatment-related allergic reaction but experienced reduction of colitis. Two patients did not respond to tocilizumab; one patient experienced worsening of diarrhea on day 12 (advanced from grade 1 to grade 2), and one with stable symptoms was later diagnosed with microscopic colitis; both patients were then treated with glucocorticoids. Six patients had endoscopic and histologic improvements without glucocorticoids (table 3, online supplemental figures S3,S4). Six patients showed radiological improvements. A follow-up colonoscopy was performed on three patients during a second evaluation (12–16 weeks after the last tocilizumab infusion, table 3). All three were still in remission of colitis.

Five patients with arthritis required local treatment at tocilizumab initiation. Within 8 weeks, none required arthrocentesis and intra-articular glucocorticoids; however, one patient treated with concomitant ICIs and tocilizumab did not achieve any clinical benefit from tocilizumab and shifted to systemic glucocorticoids on day 24. In total, 10 of 11 patients had reduced symptoms of arthritis (table 2).

Treatment exposure

All patients received ≥1 dose of tocilizumab. The median number of infusions and treatment duration were 5 (1–10) and 24 weeks (2–36), respectively. Three patients discontinued tocilizumab after one infusion (worsening symptoms (n=2) or an infusion-related reaction (n=1)). One patient was readministered with tocilizumab owning arthritis relapse. Within 24 weeks, 10 patients received concomitant ICI and tocilizumab therapy with a median duration of 10 weeks (3–65) (figure 1).

Safety

Sixteen of 20 (80%) patients had AEs of any grade related to tocilizumab, none of which were fatal. Five patients (25%) experienced grades 3–4 treatment-related AEs (TRAEs): Neutropenia (n=2, one of them developed new-onset hypophysitis and severe infection/septic shock); thrombocytopenia (n=1); colitis with ulcerations (n=1), and allergic reaction (n=1) requiring glucocorticoids and observation at the hospital (table 4).

Inflammatory markers

An increase in IL-6 level was observed in all patients regardless of response as expected. Plasma levels of IL-8, IL-17, CRP, and YKL-40 decreased mainly in patients who responded to treatment. One patient with glucocorticoid-refractory colitis had a notable decrease in IL-17 levels, correlating with clinical response (figure 2, online supplemental figures S5,S6).

Cancer status

From tocilizumab initiation and during the study period of 24 weeks, six of 20 (30%) patients experienced cancer progression (data are shown in figure 1, for further description, see online supplemental results and online supplemental figures S7A–B and S8A–B).

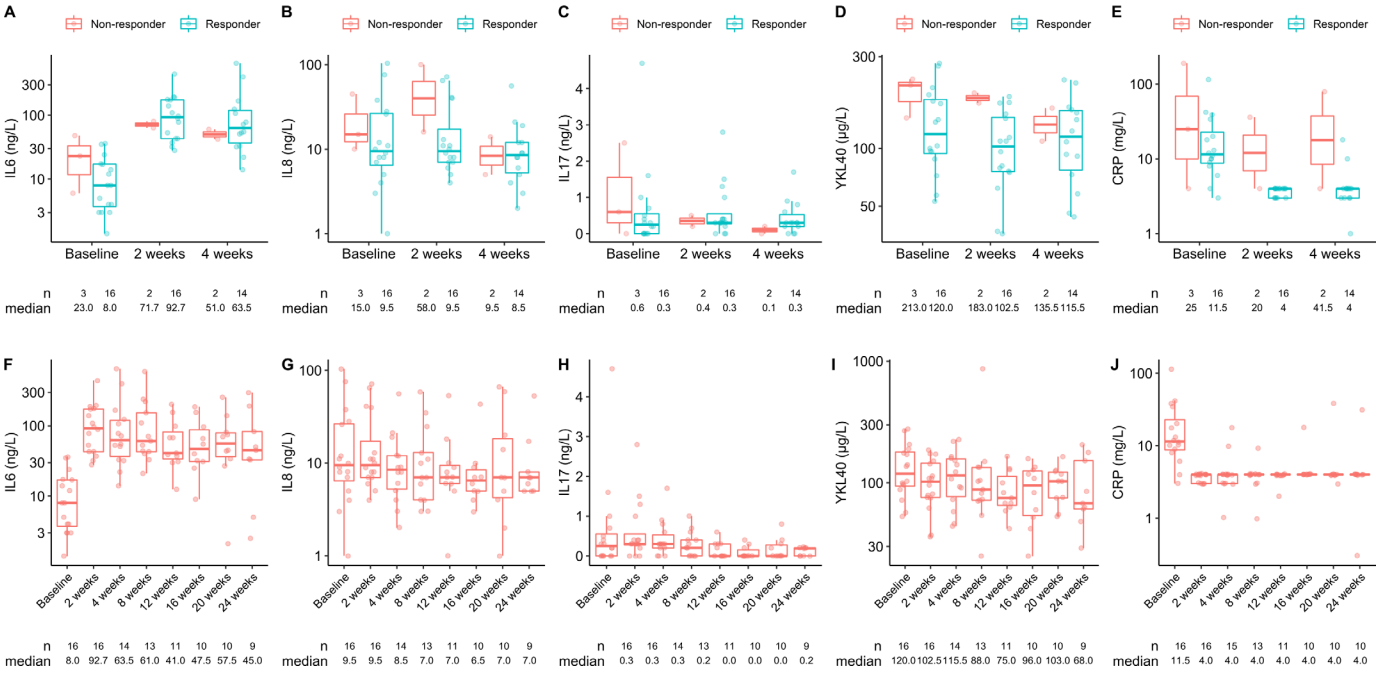


Figure 2 Plasma concentrations of IL-6, IL-8, IL-17, YKL-40, and C reactive protein (CRP). (A–E) Plasma concentrations of IL-6, IL-8, IL-17, YKL-40, and CRP during the first 4 weeks of tocilizumab among responders and non-responders. (F–J) Plasma concentrations of IL-6, IL-8, IL-17, YKL-40, and CRP in responding patients. IL, interleukin; YKL-40, chitinase-3-like-protein 1.

DISCUSSION

To the best of our knowledge, this is the first study to demonstrate that tocilizumab, an IL-6-receptor inhibitor, can be safely used to treat ICI-induced colitis/diarrhea and arthritis. The majority (15/19, 79%) of evaluable patients had a reduction of CTCAE grade by ≥1 within 8 weeks and additional one had ≥1 grade reduction at 10 weeks. Thus, the threshold for primary efficacy was met. At week 24, symptom reduction was experienced by 16 (84%) patients and durable responses by 12 patients, including complete remission of symptoms in 10 patients. During this treatment, half of the patients were able to continue ICIs.

Importantly, we observed acceptable toxicity during ICIs and tocilizumab combination therapy; however, colon ulceration and an increased risk of infection should be considered, especially in patients with cancer. In this study, only patients previously treated with chemotherapy developed neutropenia and thrombopenia, both well-known TRAEs. Nevertheless, we cannot exclude these two severe above-mentioned events could be influenced by ICI exposure or combination with tocilizumab. One patient achieving clinical benefit permanently discontinued tocilizumab due to an infusion-related reaction after the first infusion. Hypersensitivity reactions related to tocilizumab have been reported in <1% of patients.[28] It is unknown if ICI-treated patients are more prone to develop hypersensitive drug reactions compared with ICI-naïve patients; however, ICIs might activate drug-responsive T-cells, which are effectors of hypersensitivity.[29]

The use of tocilizumab to manage irAEs has been previously investigated in retrospective studies and case series with promising results. Stroud *et al* reported clinical improvements in 27 of 34 patients treated with tocilizumab and glucocorticoids for severe pneumonitis, serum sickness, and cerebritis.[21] The benefit of tocilizumab for ICI-induced arthritis, polymyalgia rheumatica, myositis, myocarditis, CRS, and hemophagocytic syndrome has been reported.[22 24 30] Recently, tocilizumab was successful in treating multiple irAEs and preventing flare of pre-existing autoinflammatory diseases in 21 of 22 patients with melanoma.[23] In our study, two patients experienced worsening of colitis and arthritis after one tocilizumab infusion (on day 12 and day 24, respectively). We cannot exclude the possibility that a more prolonged treatment exposure to tocilizumab is required due to increased tocilizumab clearance. In patients with inflammatory signatures of CAR T-cell induced CRS, tocilizumab infusion is usually repeated if symptoms do not improve within 48 hours.[20 31] One patient with stabile symptoms was diagnosed with microscopic colitis, a histopathological subgroup of ICI-induced colitis, and did not respond to tocilizumab treatment. The patient was then effectively treated with budesonide, as reported by Hughes *et al*.[32]

Although the antitumoral efficacy of ICIs has been extensively studied, crucial concerns regarding resumption of ICIs following moderate to severe irAEs, concomitant immunosuppressive therapies (especially in patients with pre-existing autoimmune diseases), and management of glucocorticoid-refractory irAEs are arising. However, no controlled trials have thus far defined the strategies for the effective management of specific irAE, and international guidelines are primarily based on retrospective cohorts, case series, and case reports; especially guidelines for treating glucocorticoid-dependent or -refractory cases are mainly based on expert opinions.[8 9 33] In our study, increasing levels

of IL-6 were observed in all patients due to blockade of the IL-6 receptors while levels of IL-8, IL-17, CRP, and YKL-40 decreased in responding patients. We noticed a patient with glucocorticoid-refractory colitis, treated with infliximab twice with minimal efficacy, achieved complete remission of symptoms after tocilizumab treatment. This response was paralleled by a decrease of a high circulating level of IL-17 before treatment, suggesting that cytokine levels are potential biomarkers in patients with irAEs refractory to standard treatment options. Early intervention with an immunosuppressive agent is reported to lead to more favorable outcomes.[34] Furthermore, adding a glucocorticoid-sparing therapy, especially in long-term irAEs, may dampen the risk of glucocorticoid-induced AEs. Currently, infliximab and vedolizumab are the preferred second-line and third-line treatment options for ICI-induced colitis.[35 36] However, ustekinumab (anti-IL-23/12), tofacitinib (a JAK inhibitor), and fecal microbiota transplantation may be effective for the treatment of refractory colitis.[37–39] Loperamide 'as needed' was allowed in this study; however, it is debated if loperamide should be withdrawn in severe colitis to prevent a potential risk of toxic colon dilatation.[40 41] In addition, CMV infection should be excluded in glucocorticoid-refractory cases, as we did in this study.[42]

Glucocorticoids are the first choice of therapy for rheumatologic AEs triggered by ICIs and usually long-term administration is required. No specific biological disease-modifying antirheumatic drugs have shown superiority, and treatment with TNF-inhibitors may require repeated administration with unknown influence on the antitumor response.[43] However, concomitant treatment with ICIs and TNF-inhibitors is being studied (NCT03293784).[44] The antitumor effect of tocilizumab was not an endpoint in this study. However, we observed cancer disease control in majority of included patients at 24 weeks. Thus, despite the small population size, tocilizumab did not seem to affect negatively the anticancer responses induced by ICIs; similar to previous reports.[23 45] Clinical trials of tocilizumab (NCT04940299, NCT04258150, NCT04375228, and NCT04691817) on anticancer responses and irAEs are ongoing.

The limitations of this study were the lack of a control group and the small population size. Thus, we cannot exclude that the observed reduction of symptoms was related to the natural course of irAEs, delayed biological effect of ICI treatment, or intra-articular glucocorticoids and other supportive agents being used. However, few data on these subjects are available making this study important as a first starter. We may also have selected patients with favorable outcomes because patients had to go through a 14-day long screening period if shifted from glucocorticoids. Also, low statistical power may increase the risk of spurious findings. We included a broad spectrum of ICI regimens and cancer types, which may have skewed outcomes. The variable duration of symptoms up to inclusion suggested a heterogeneous cohort, limiting the generalizability of results. Moreover, irAEs may be caused by several relatively unknown mechanisms, and some may like to respond better to treatment than others. The strengths of this study were its prospective study design and extensive multidisciplinary workup. In addition, we supplied measurements of circulating cytokines and YKL-40. Larger comprehensive cohorts, including controls testing tocilizumab or alternative strategies for irAEs are needed. Still, a central concern is the sparsity of data related to safety and efficacy of treating irAEs with glucocorticoids and immunosuppressive drugs, including their effects on anticancer responses. However, whether immunosuppression related to tocilizumab is more acceptable than glucocorticoids is unknown. The CTCAE grading of irAEs should also be more specific and include imaging, endoscopy, and histopathology results. In addition, many patients treated with ICIs experience multiorgan toxicity.[9] Therefore, a guide to multidisciplinary team building and management would be an oncological imperative of essential value. Future studies incorporating blood-based biomarkers in irAEs, as well as selecting other steroid-sparing agents are warranted. Finally, moving anti-IL-6 agents to first-line therapy for the management of the new-onset irAEs should be studied from a cost-effective perspective as it would have significant implications.

CONCLUSIONS

Tocilizumab showed promising clinical efficacy and a manageable safety profile in 16 of 19 (84%, 95% CI 60 to 97%) patients experiencing ICI-induced colitis and/or arthritis. Half of the patients successfully continued ICIs concomitant with tocilizumab. Future prospective studies of organ-specific irAEs managed with glucocorticoids as a standard approach and experimental therapies, including randomization, are warranted to refine treatment guidelines.

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