Immune Effector Cell–Associated Enterocolitis (IEC-EC) Incidence and Characterization in Cilta-cel–Treated Patients With RRMM in CARTITUDE Clinical Studies

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Key Takeaways

- IEC-EC is characterized by diarrhea/altered stool consistency, with a median onset of 67 days (range, 12–214) after cilta-cel infusion in this cohort; infection work-up and esophagogastroduodenoscopy with biopsies (particularly duodenal) are critical to identify IEC-EC
- In this study, 4/6 IEC-EC cases resolved, with patients receiving supportive care or steroids
- In the real-world, a short course of steroids, biologic agents, and/or T-cell directed therapies have shown benefit in a subset of patients with IEC-EC[3,5]

Conclusions

- Across 4 RRMM clinical trials of cilta-cel, IEC-EC incidence was 1.2%
- CAR-T–mediated GI plasma cell depletion and immune dysregulation may play a role in the etiology
- Increased awareness and earlier diagnosis may improve management of IEC-EC and enhance likelihood of reversibility

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Introduction

- Ciltacabtagene autoleucel (cilta-cel) provides significant treatment-free progression-free survival (PFS) and overall survival (OS) benefit in relapsed/refractory multiple myeloma (RRMM) as early as the second line of therapy (LOT),[1,2] with one-third of heavily pretreated patients disease and treatment free beyond 5 years, suggesting potential cure[2]
- Immune effector cell–associated enterocolitis (IEC-EC has been described as severe and/or prolonged diarrhea occurring 1–3 months after chimeric antigen receptor (CAR)-T cell infusion and was not identified in CARTITUDE clinical trials, as it is a recently recognized adverse reaction[3,4]
- In a real-world study, the incidence of IEC-EC in patients with RRMM treated with cilta-cel was 2%[3]
- Mechanisms underlying IEC-EC are not fully defined and characterization of features of IEC-EC after cilta-cel could aid early diagnosis and management
- Here, we summarize the incidence and features of IEC-EC in patients with RRMM across cilta-cel clinical trials

Methods

Clinical characterization

- Retrospective analysis of cilta-cel patients with RRMM from the Global Medical Safety database was performed to identify cases consistent with IEC-EC in CARTITUDE-1, CARTITUDE-2 (cohorts A, B, and C), CARTITUDE-4, and CARTIFAN-1 (N=483)
- Patients were classified as having IEC-EC if they had grade ≥3 diarrhea, defined as having ≥2 of the following:
  - Serious or prolonged (≥3 weeks) diarrhea
  - No direct infectious etiology for diarrhea
  - Gastrointestinal (GI) samples with crypt dropout, apoptotic changes, villous blunting, and/or T-cell infiltration (if biopsied)
- Patients with other GI symptoms either did not meet the criteria for IEC-EC or had diarrhea due to infection or GI bleeding
- Cases occurring from Aug 28, 2018, to Jan 16, 2025, were analyzed

Correlative biomarker analyses

- CAR-T cell expansion and persistence, immune cell composition, cytokines, and inflammatory markers were assessed by flow cytometry
- *P* values of comparative analyses were unadjusted and determined using the Wilcoxon test

Pathology

- Centralized pathomorphological review and immunohistochemical analysis was conducted from patients experiencing GI symptoms after cilta-cel
- Peripheral CAR-T cell expansion/persistence and immune cell composition was determined by the Wilcoxon test in patients who developed IEC-EC, in those with other GI symptoms, and in GI symptom-free control patients
  - Displayed are nominal *P* values without multiple testing correction

Results

Clinical course and management of patients with IEC-EC

- Of 483 treated patients with RRMM, 6 (1.2%) developed IEC-EC (**Tables 1** and **2**)
- All 6 patients with IEC-EC had achieved complete response or better after cilta-cel
- None of the patients with IEC-EC developed cranial nerve palsy or IEC-parkinsonism

Table 1: Baseline characteristics of patients with IEC-EC

	IEC-EC (N=6)
Median age, years	62
Male, n/N	5/6
Median weight, kg	86.5
ECOG PS 1, n/N	3/6
≥3 prior LOT, n/N	4/6
Bone marrow plasma cells ≥60%, n/N	1/6
High-risk cytogenetics, n/N	4/6

High-risk cytogenetics was defined as the presence of del(17p), t(14;16), or t(4;14). ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2: IEC-EC cases in patients in the CARTITUDE studies

Case	IEC-EC onset, day	Max Grade	ID work-up	IgG,[a] g/L	IgA,[a] g/L	IgM,[a] g/L	IEC-EC duration	Resolved[b]	Treatment	Duration of steroids for IEC-EC	Weight loss
1	61	3	Neg	9.68–6.68	<0.25	<0.20	62 days	Yes	Supportive care	NA	Grade 1
2	119	3	Neg	<0.70	<0.25	<0.20	33 days	Yes	Supportive care	NA	Not reported
3	214	3	Neg	3.77[c]	<0.25	<0.20	>5 weeks	No	Methyl-prednisolone	16 days	Grade 2
4	12	3	Neg	0.89[d]	<0.25	<0.20	>19 weeks	No	Cyclosporine Prednisone	85 days	Grade 1
5	73	3	Neg	1.09[e]	<0.25	<0.20	154 days	Yes	Budesonide	100 days	Grade 2
6	41	3	Neg	3.85–11.40	1.86[f] to <0.28	<0.20	168 days	Yes	FMT; supportive care	NA	Grade 2 (D68–D100) Grade 3 (D100–D340)

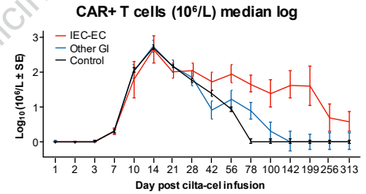
[a]Around IEC-EC onset. [b]Resolution as reported by the investigator. [c]Data from day 196 are presented. [d]Data from day 27 are presented. [e]Data from day 59 are presented. [f]IgA subtype. D, day; FMT, fecal microbiota transplant; ID, infectious disease; Ig, immunoglobulin; max, maximum; NA, not applicable; neg, negative.

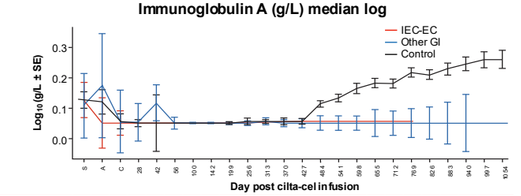
- Median IEC-EC onset was 67 days (range, 12–214) after cilta-cel infusion
- IEC-EC treatment included steroids (3/6) and cyclosporine (1/6)
- Intravenous immunoglobulin was administered to 4/6 patients who developed IEC-EC
- 2 patients with IEC-EC achieved partial response to bridging therapy following 3 cycles of pomalidomide, bortezomib, and dexamethasone (case 3) or daratumumab, pomalidomide, and dexamethasone (case 5)
  - Other patients with IEC-EC had stable disease (case 2), minimal response (case 4), and no effect (cases 1 and 6)
- 4 of 6 IEC-EC cases resolved; 2 patients experienced persistent symptoms until death due to multiorgan failure and COVID-19

CAR+ T cells in blood of patients with IEC-EC

- CAR+ T-cell persistence in peripheral blood was longer in patients with IEC-EC than in GI symptom-free control patients and was comparable to persistence in patients with other GI symptoms (**Figure 1**)
- Patients with IEC-EC experienced prolonged depletion of IgA and B cells, and had lower levels of B cells and higher levels of inflammatory cytokines (eg, interleukin-6) at onset compared with the GI symptom-free control group at a comparable time
- There was no increased T-cell receptor clonality in peripheral blood associated with IEC-EC or GI symptom onset

Figure 1: CAR+ T cells and immunoglobulin A in peripheral blood based on presence of IEC-EC[a]





No. of patients	1	2	3	7	10	14	21	28	42	56	78	100	142	199	256	313
IEC-EC[a]	5	1	1	5	5	4	5	4	4	5	5	2	5	3	2	2
Other GI	23	8	3	22	20	21	21	18	19	20	20	21	12	19	16	15
Control	190	79	21	185	178	190	185	187	189	180	176	160	139	150	139	137

No. of patients	68	A	C	28	42	56	100	142	199	256	313	370	427	484	541	598	655	712	769	826	883	940	997	1054
IEC-EC[a]	5	3	5	4	1	5	4	5	4	3	2	1	1	1	1	1	1	1	0	0	0	0	0	0
Other GI	23	15	23	20	2	20	22	21	20	20	18	18	17	17	16	15	12	11	11	10	8	4	3	2
Control	197	123	192	196	8	187	182	186	180	176	169	165	147	143	144	129	127	114	110	101	76	55	42	29

[a]Data not available for case 6. A, apheresis; C, conditioning; S, screening.

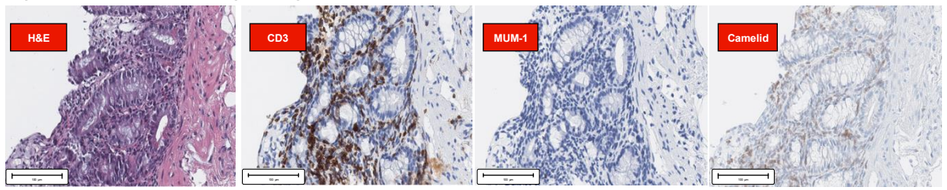
Histopathology of GI biopsies from patients experiencing IEC-EC

- Plasma cells were largely absent from stomach, duodenum, and colon biopsies (**Table 3** and **Figure 2**)
- Signs of injury were most common in the duodenum (66% of specimens), and also present in the colon (40% of specimens) (**Table 3** and **Figure 2**)
- CAR-T cells were observed in the lamina propria of the duodenum and did not appear to be associated with epithelial damage (**Figure 2**)

Table 3: Aberrant findings by anatomical region (biopsy site)[a]

Biopsy site	n	Architectural distortion	Apoptotic bodies	Metaplasia	Regenerative changes	Intraepithelial lymphocytosis	Malabsorption pattern	Plasma cells present	CAR-T cells present
Stomach	2	0	1	0	0	0	0	0	1
Duodenum	3	1	2	2	0	0	1	0	2
Colon	5	0	3	0	2	3	0	0	2

Figure 2: Representative histological images of the duodenum from a patient with IEC-EC



Immunohistochemical staining: H&E for cytoplasm and nuclei; CD3 for T cells; MUM-1 for activated T cells, plasma cells, and late germinal center B cells; camelid for CAR-T cells. H&E, hematoxylin and eosin; MUM-1, multiple myeloma oncogene 1.

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