Brief Communication

Role of Infliximab in Immune Checkpoint Inhibitor-Induced Pneumonitis

Kathryn A. Lai,[1] Ajay Sheshadri,[2] Andres M. Adrianza,[2] Mikel Etchegaray,[3] Diwakar D. Balachandran,[2] Lara Bashoura,[2] Vickie R. Shannon,[2] Saadia A. Faiz[2]

[1]Divisions of Pulmonary, Critical Care Medicine, and Sleep Medicine, McGovern Medical School at University of Texas Health, Houston, Texas, USA
[2]Department of Pulmonary Medicine, Division of Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA
[3]Department of General Internal Medicine, Division of Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Address correspondence to Saadia A. Faiz (safaiz@mdanderson.org)

Sources of Support: This research is supported in part by the National Institutes of Health through MD Anderson's Cancer Center Support Grant (CA016672) and a grant to Ajay Sheshadri (NIH/NIAID K23 AI117024). Conflict of Interest: None.

Received: Jun 18, 2020; Accepted: Jul 29, 2020

Lai KA, Sheshadri A, Adrianza AM, Etchegaray M, Balachandran DD, Bashoura L, Shannon VR, Faiz SA. Role of infliximab in immune checkpoint inhibitor-induced pneumonitis. *J Immunother Precis Oncol*. 2020; 3:172–174. DOI: 10.36401/JIPO-20-22.

ABSTRACT

Introduction: Since immune checkpoint inhibitor (ICI) blockade has become standard therapy for many cancers, immune-related adverse events (irAEs) have increased. ICI-pneumonitis is infrequent but potentially fatal. In cases not responsive to corticosteroids, additional immunosuppression is recommended. Data for use of infliximab in ≥ grade 3 pneumonitis is sparse. **Materials and Methods:** A retrospective review of patients who received infliximab for ICI-pneumonitis from March 2016 to October 2018 was performed. Clinical characteristics were reviewed. **Results:** Nine patients (44% women) with ≥ grade 3 pneumonitis were included. Concurrent/prior irAEs were present in 55%. Bronchoscopy was performed in 67%. Median corticosteroid dose was 1.2 mg/kg prior to infliximab, and time from administration of corticosteroids to infliximab ranged from 2 to 34 days. Four patients improved, but the remainder died. **Conclusion:** We report improvement of ICI-pneumonitis with infliximab in 4 out of 9 patients in a small, retrospective cohort. Further prospective randomized controlled trials are needed.

Keywords: immunotherapy, cancer, anti-PD-1, infliximab, immune-related adverse events, pneumonitis

INTRODUCTION

Immune checkpoint inhibitor (ICI) blockade has become the standard of care for the treatment for many cancers.[1–3] As clinicians become more familiar with ICI agents, immune-related adverse events (irAEs) are increasingly recognized as drivers of treatment-related morbidity and mortality.[4] The irAEs associated with ICIs differ from the toxicities observed with conventional cytotoxic chemotherapy in mechanism and timing and are serious, often treatment-limiting complications.[5] The overall incidence of ICI-pneumonitis based on clinical trial data is 2.5%–5.0% with monotherapy and 7%–10% with combination therapy, with high-grade (≥ grade 3) events occurring in 1%–2% of patients.[6] Despite the low incidence, pneumonitis is the most common cause of ICI-related death.[7]

Management of irAEs is currently guided by expert consensus from the Society of Immunotherapy of Cancer and the American Society of Clinical Oncology based on the Common Criteria for Adverse Events grade.[8,9] Close observation or withholding ICI therapy may be sufficient in patients that are asymptomatic. In those with respiratory symptoms (≥ grade 2), in addition to radiographic changes, corticosteroids are initiated, with a gradual taper over weeks.[9] When respiratory symptoms are severe and not responsive to corticosteroid therapy, then additional immunosuppressive therapy may be added. However, the risk of developing a new infection or exacerbating an existing infection looms. In the largest series of ICI-pneumoni-

Table 1.—Patient characteristics receiving infliximab for grade 3 and 4 pneumonitis

Case	Age, Years	Sex	Cancer	Immunotherapy	Corticosteroid, mg/kg*	Time, Days^	Ventilatory Support, FiO2%	irAEs	Bronchoscopy, Lymphocytes, %	Outcome
1	66	M	Melanoma	Ipilimumab	1.2	2	Nasal cannula, 24%	–	No	Improved
2	66	M	Pancreatic	Ipilimumab	1.3	5	High-flow, 45%	Hepatic[&]	No	Improved
3	52	F	AML	Ipilimumab, nivolumab	3.3	9	High-flow, 60%	–	Yes[‡]	Improved
4	69	F	AML	Ipilimumab, nivolumab	1.1	7	MV, 90%	Dermatologic, gastrointestinal	Yes[‡]	Improved
5	79	M	AML	Nivolumab	2.4	34	High-flow, 50%	Renal	Yes, 13	Death[+]
6	72	M	AML	Ipilimumab, nivolumab	1.1	Chronic	High-flow, 30%	Hematologic	Yes, 26	Death[+]
7	72	F	MDS	Ipilimumab, nivolumab	2.0	2	BiPAP, 70%	Dermatologic	Yes, 18	Death
8	68	F	Lung	Nivolumab	0.8	9	High-flow, 75%	–	No	Death
9	61	M	Urothelial	Nivolumab	1.2	7	High-flow, 75%	–	Yes[‡]	Death

AML: acute myeloid leukemia; MDS: myelodysplastic syndrome; MV: mechanical ventilation; BiPAP: bi-level positive airway pressure
*Maximal dosage (all patients were initiated on intravenous methylprednisone, and those that improved were transitioned to oral prednisone)
^Time from steroid administration to infliximab dosing
[+]Initially had improvement
[&]irAE occurred prior to pneumonitis
[‡]No bronchoalveolar lavage cell count and differential performed

tis, Naidoo and colleagues[4] reported 43 cases, of which 72% were grades 1 and 2, and 86% improved with withholding therapy or corticosteroid therapy. Five patients worsened and were treated with either infliximab or infliximab with cyclophosphamide, and of those, three died from sepsis. Unfortunately, data for the treatment of grade 3 and 4 ICI-pneumonitis remain sparse.[10,11] We retrospectively evaluated patients that received infliximab for ICI-induced pneumonitis in our institution.

METHODS

We performed a retrospective chart review on all patients who received infliximab at our institution between March 2016 and October 2018. Only those that received infliximab for ICI-induced pneumonitis were included. All cases were reviewed by three experts. Patient demographics, oncologic history, and radiographic and laboratory data were extracted from the electronic medical record. The study was approved by the Institutional Review Board (PA15-0917).

RESULTS

Ninety-four patients were identified, but only 10 (11%) received infliximab for pneumonitis and included in our study. Patient characteristics are detailed in Table 1 for those who developed pneumonitis. One patient had a bronchoscopy revealing *Pneumocystis* pneumonia 9 days prior to infliximab, so this patient was excluded after review by our panel. Five patients received monotherapy with programmed cell death-1 (PD-1; 33%) or cytotoxic T-lymphocyte antigent-4 (CTLA-4)-CD28 (22%), and four patients received combination therapy with PD-1 and CTLA-4 (44%).

All patients were hospitalized for grade 3–4 pneumonitis and received broad-spectrum antibiotics and high-dose corticosteroid therapy. After QuantiFERON tests were negative, infliximab was given as a single dose (5 mg/kg) for persistent hypoxic respiratory insufficiency (Table 1). Five patients had concurrent active irAEs, while one patient had a prior irAE. Radiographic imaging revealed bilateral diffuse ground glass infiltrates in all patients. Pulmonary embolism was found in one patient, and preexisting lung disease was present in one patient (emphysema). Bronchoscopy was performed in six patients, but three were deferred due to significant oxygen requirement. Four patients had sustained clinical improvement in respiratory status, with complete resolution of radiographic findings in two patients, near-complete resolution in one patient, and one who did not receive follow-up imaging. Time from infliximab dosing to decreased oxygen requirement ranged from 1 to 5 days. Of the remaining five patients, three died from progression of their malignancy and two died from multiorgan failure.

DISCUSSION

Infliximab was used to treat $\geq$ grade 3 ICI-induced pneumonitis in nine patients. Five patients received monotherapy with either PD-1 or CTLA-4, and four had combination therapy with PD-1 and CTLA-4. All patients received empiric antimicrobial therapy and high-dose corticosteroids prior to infliximab. Concurrent or prior

irAEs were present in 55%. Bronchoscopy was performed in 67%. Four patients improved, but the infliximab was given at varying times in relation to presentation.

Use of tumor necrosis factor-α (TNF-α) inhibitors has improved disease control in many conditions, including rheumatoid arthritis and inflammatory bowel disease. Their success in autoimmune-mediated conditions has led to the extrapolation for treatment of irAEs. For example, ICI-colitis shares common histologic and pathophysiological features with inflammatory bowel disease, and thus use of infliximab has become standard after 2–3 days of corticosteroids.[12] In comparison, the evidence for use of TNF inhibitors in pulmonary disease is limited, and there has been a mixed response in reports of sarcoidosis and pulmonary fibrosis based on case reports and small case series.[13] In our cohort, high-grade ICI-pneumonitis treated with infliximab resulted in resolution of respiratory insufficiency in four patients. However, we cannot infer a 44% response rate attributed to infliximab alone due to the lack of a proper comparator. We can infer that in 55% of our cohort, patients had no improvement in their breathing, suggesting that further work is necessary to identify appropriate second-line therapies for ICI-pneumonitis. The lack of improvement in the remaining five may be multifactorial, including new or worsened underlying infection, disease progression, delay in infliximab dosage, or acute respiratory distress syndrome. In our current practice, we try to evaluate for infection with bronchoscopy when feasible. In those that we consider high suspicion for ICI-pneumonitis, a QuantiFERON test was ordered, and corticosteroids were administered. If improvement was not seen within 48–72 hours, then a single dose of infliximab was administered.

Our study has limitations inherent to most retrospective studies. Our sample size was small, and uncontrolled factors existed in our study, including different underlying cancers, variations in corticosteroid dosing, and nonuniform time to infliximab administration. Much of the variability in treatment was because it was performed at the discretion of the treating physicians and not by a standardized protocol. Our data were obtained through the electronic medical record, which captures all patients who received infliximab during this time period; however, we could not capture patients who received infliximab outside of our institution. We were unable to answer several key questions, including risk factors for the development of $\geq$ grade 3 pneumonitis, optimal timing for infliximab dosing, and the utility of bronchoalveolar lavage/serum biomarkers. Larger prospective controlled studies systematically evaluating the efficacy of infliximab in ICI-pneumonitis are needed.

In conclusion, we report improvement of ICI-pneumonitis with infliximab in four out of nine patients in a small, retrospective cohort. Our findings require validation in a prospective, randomized controlled trial.

References

1. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med*. 2016;375:1823–1833.
2. Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2015;16:522–530.
3. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med* 2015;373:1803–1813.
4. Naidoo J, Wang X, Woo KM, et al. Pneumonitis in patients treated with anti-programmed death-1/programmed death ligand 1 therapy. *J Clin Oncol*. 2017;35:709–717.
5. Bajwa R, Cheema A, Khan T, et al. Adverse effects of immune checkpoint inhibitors (programmed death-1 inhibitors and cytotoxic T-lymphocyte-associated protein-4 inhibitors): results of a retrospective study. *J Clin Med Res*. 2019;11:225–236.
6. Sears CR, Peikert T, Possick JD, et al. Knowledge gaps and research priorities in immune checkpoint inhibitor-related pneumonitis. An official American Thoracic Society research statement. *Am J Respir Crit Care Med*. 2019;200:e31–e43.
7. Wang DY, Salem JE, Cohen JV, et al. Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis. *JAMA Oncol*. 2018;4:1721–1728.
8. Puzanov I, Diab A, Abdallah K, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer*. 2017;5:95.
9. Brahmer JR, Lacchetti C, Schneider BJ, et al. 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.
10. Martins F, Sykiotis GP, Maillard M, et al. New therapeutic perspectives to manage refractory immune checkpoint-related toxicities. *Lancet Oncol*. 2019;20:e54–e64.
11. Bade BC, Possick JD. Pulmonary complications of immunotherapy. *Clin Chest Med*. 2020;41:295–305.
12. Johnson DH, Zobniw CM, Trinh VA, et al. Infliximab associated with faster symptom resolution compared with corticosteroids alone for the management of immune-related enterocolitis. *J Immunother Cancer*. 2018;6:103.
13. Khasnis AA, Calabrese LH. Tumor necrosis factor inhibitors and lung disease: a paradox of efficacy and risk. *Semin Arthritis Rheum*. 2010;40:147–163.