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Shorter versus longer corticosteroid duration and recurrent immune checkpoint inhibitor-associated AKI

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ABSTRACT

Background Corticosteroids are the mainstay of treatment for immune checkpoint inhibitor-associated acute kidney injury (ICPi-AKI), but the optimal duration of therapy has not been established. Prolonged use of corticosteroids can cause numerous adverse effects and may decrease progression-free survival among patients treated with ICPis. We sought to determine whether a shorter duration of corticosteroids was equally efficacious and safe as compared with a longer duration.

Methods We used data from an international multicenter cohort study of patients diagnosed with ICPi-AKI from 29 centers across nine countries. We examined whether a shorter duration of corticosteroids (28 days or less) was associated with a higher rate of recurrent ICPi-AKI or death within 30 days following completion of corticosteroid treatment as compared with a longer duration (29–84 days).

Results Of 165 patients treated with corticosteroids, 56 (34%) received a shorter duration of treatment and 109 (66%) received a longer duration. Patients in the shorter versus longer duration groups were similar with respect to baseline and ICPi-AKI characteristics. Five of 56 patients (8.9%) in the shorter duration group and 12 of 109 (11%) in the longer duration group developed recurrent ICPi-AKI or died (p=0.90). Nadir serum creatinine in the first 14, 28, and 90 days following completion of corticosteroid treatment was similar between groups (p=0.40, p=0.56, and p=0.89, respectively).

Conclusion A shorter duration of corticosteroids (28 days or less) may be safe for patients with ICPi-AKI. However, the findings may be susceptible to unmeasured confounding and further research from randomized clinical trials is needed.

INTRODUCTION

Immune checkpoint inhibitor-associated acute kidney injury (ICPi-AKI) is an increasingly recognized immune-related adverse event (irAE) that occurs in 2–5% of patients treated with ICPis.[1 2] Patients who develop ICPi-AKI often have their ICPi therapy interrupted or permanently discontinued.[3] They are also typically treated with immunosuppression, usually in the form of high-dose corticosteroids (CS).[3]

Despite their efficacy in treating irAEs, including ICPi-AKI, CS can result in hyperglycemia, weight gain, edema, fractures, gastrointestinal bleeds, infection, and other adverse events.[4 5] Accordingly, defining the optimal duration of treatment with CS is critical to minimizing its side effect profile, as well as allowing for timely ICPi rechallenge, if indicated. Simultaneously, there is concern that premature discontinuation of CS might increase the risk of ICPi-AKI recurrence. There are few data available to guide clinicians in choosing the duration of CS for ICPi-AKI, and treatment duration varies widely in clinical practice.[3]

To address this knowledge gap, we used data from an international multicenter cohort study of adults with ICPi-AKI to examine whether shorter duration of CS treatment is associated with a higher risk of recurrent ICPi-AKI as compared with longer duration.

METHODS

Study design

We previously described the clinical features, treatment, and outcomes of 429 adults diagnosed with ICPi-AKI between January 1, 2012, and December 31, 2020, from 30 sites across 10 countries.[3] The cohort consisted of patients with AKI directly attributable to ICPi therapy (online supplemental table S1). AKI severity was staged according to the Kidney

Disease: Improving Global Outcomes criteria (online supplemental table S2).[6] In the current analyses, we included patients who initiated treatment with high-dose CS (≥40 mg daily in prednisone equivalents) within 14 days following ICPi-AKI diagnosis and had their CS tapered to ≤10 mg daily of prednisone equivalents within 12 weeks (84 days) following CS initiation. Eighty-four days was selected as the cut-off for the long duration group based on the distribution of the data, with the vast majority of patients tapered within this time frame (online supplemental figure S1). We excluded the following groups of patients: those already receiving treatment with CS (>10 mg daily of prednisone equivalents) at the time of ICPi-AKI diagnosis; those with a primary histopathologic lesion other than acute tubulointerstitial nephritis (ATIN); those treated with non-CS immunosuppression at the time of ICPi-AKI diagnosis; and, to avoid immortal time bias, those who died within 28 days of initiating CS (figure 1).

Primary objective and definition of recurrent ICPi-AKI

The primary objective was to determine the incidence and time to recurrent ICPi-AKI following completion of CS among patients who received a shorter duration (<28 days) versus a longer duration (29–84 days) of CS treatment. CS treatment was considered to be completed once the dose was tapered to ≤10 mg per day of prednisone equivalents. Recurrent ICPi-AKI was defined as meeting each of the following criteria: (1) an increase in serum creatinine (SCr) ≥50% compared with the value at completion of CS, or receipt of kidney replacement therapy; (2) the AKI was directly attributable to the ICPi by the treating provider; and (3) the AKI was treated with re-initiation or escalation of CS. To focus on unprovoked recurrence of ICPi-AKI (as opposed to recurrence of ICPi-AKI following ICPi rechallenge), we limited the assessment of the outcome to the first 30 days following completion of CS treatment. To account for death as a competing risk, we examined a composite outcome of recurrent ICPi-AKI or death in the 30 days following completion of CS treatment.

Statistical analysis

We compared baseline characteristics between patients in the shorter versus longer CS treatment groups. Categorical data were compared using χ^2 or Fisher's exact test, as appropriate. Continuous data were compared using Student's t-test or Wilcoxon rank-sum test for normally distributed and skewed data, respectively. We compared time to recurrent ICPi-AKI or death between groups using Kaplan-Meier curves and the log-rank test. We compared nadir SCr in the first 14, 28, and 90 days following completion of CS treatment between groups using the Wilcoxon rank-sum test. Finally, in a sensitivity analysis, we compared the incidence of recurrent ICPi-AKI or death between groups only in patients who had received a kidney biopsy during their initial episode of ICPi-AKI. Two-sided p values<0.05 were considered significant. Analyses were performed in SAS V.9.5 (SAS Institute).

RESULTS

Baseline characteristics

The original cohort included 429 patients with ICPi-AKI from 30 sites across 10 countries. After applying the exclusion criteria, the cohort for the current analyses consisted of 165 patients from 29 sites across 9 countries, 56 (34%) of whom received a CS treatment duration of 28 days or less and 109 (66%) of whom received a treatment duration of 29–84 days (figure 1). Patients in the shorter versus longer

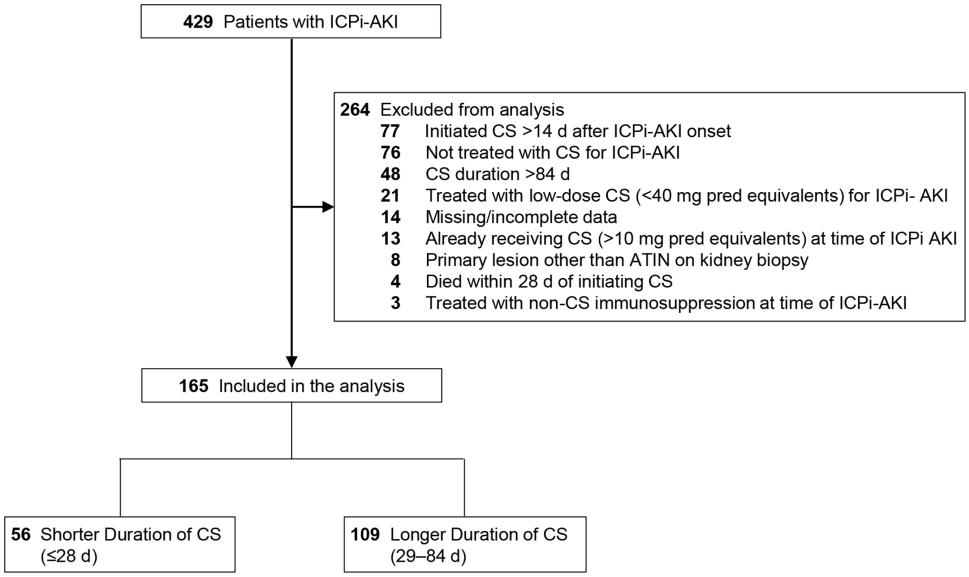

Figure 1 Flowchart. ATIN, acute tubulointerstitial nephritis; CS, corticosteroids; d, days; ICPi-AKI, immune checkpoint inhibitor-associated acute kidney injury; pred, prednisone.

Table 1 Baseline characteristics

Variable	Shorter duration of CS (n=56)	Longer duration of CS (n=109)	P value
Age at ICPi initiation, years, median (IQR)	68 (59–75)	69 (61–76)	0.51
Male, n (%)	36 (64.3)	69 (63.3)	0.99
Race, n (%)			0.84
White	47 (83.9)	95 (87.2)	
Black	4 (7.1)	3 (2.8)	
Other/unknown	5 (8.9)	11 (10.1)	
Comorbidities, n (%)			
Hypertension	36 (64.3)	73 (67.0)	0.74
Diabetes	10 (17.9)	22 (20.2)	0.84
CHF	3 (5.4)	4 (3.7)	0.69
COPD	0 (0)	17 (15.6)	<0.01
Cirrhosis	1 (1.8)	0 (0)	0.34
Body mass index, median (IQR)	26 (23–30)	28 (24–31)	0.20
Baseline eGFR,* mL/min per 1.73 m^2			
Median (IQR)	72 (58–85)	72 (60–87)	0.54
eGFR categories, n (%)			0.61
≥90	12 (21.4)	20 (18.4)	
60–89	28 (50.0)	62 (56.9)	
45–59	6 (10.7)	15 (13.8)	
<45	10 (17.9)	12 (11.0)	
Extrarenal irAE,† n (%)	26 (46.4)	57 (52.3)	0.51
Malignancy, n (%)			0.54
Lung	11 (19.6)	29 (26.6)	
Melanoma	17 (30.4)	28 (29.4)	
Genitourinary	17 (34.7)	32 (65.3)	
Other			
PPI,‡ n (%)	28 (50.0)	67 (61.5)	0.18
Combo anti-CTLA-4+anti-PD-1/PD-L1	15 (26.8)	27 (24.8)	0.85
Duration of CS, median (IQR)	21 (14–25)	46 (36–59)	<0.01

Data are shown as median (IQR) and n (%). All data are complete.
*Baseline eGFR was defined based on the closest SCr prior to ICPi initiation, and was calculated based on Chronic Kidney Disease-Epidemiology Collaboration equation.[13]
†Extrarenal irAEs were assessed prior to (>14 days) or concomitant (within 14 days before or after) with ICPi-AKI diagnosis.
‡PPIs were assessed in the 14 days preceding ICPi-AKI diagnosis.
AKI, acute kidney injury ; CHF, congestive heart failure; Combo, combination therapy; COPD, chronic obstructive pulmonary disease; CS, corticosteroids; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; eGFR, estimated glomerular filtration rate; ICPi, immune checkpoint inhibitor; irAE, immune-related adverse event; PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1; PPI, proton pump inhibitor; SCr, serum creatinine.

treatment groups were largely similar with respect to age, sex, race, malignancy type, baseline kidney function, and comorbidities (table 1).

Characteristics of initial episode of ICPi-AKI

Characteristics of the initial episode of ICPi-AKI are shown in table 2. The distribution of AKI severity was similar between patients in the shorter versus longer duration of CS treatment groups, as were urinalysis findings and urine protein studies (table 2). A total of 13 of the 56 patients (23.2%) in the shorter duration group, and 38 of the 109 patients (34.9%) in the longer duration group were biopsied, with ATIN found on all biopsies (table 2). Time from ICPi-AKI diagnosis to initiation of CS was also similar between groups. The median initial oral dose of CS was 60 mg daily in prednisone equivalents in both groups (table 2).

Recurrent ICPi-AKI or death

A total of 17 patients (10.3%) developed recurrent ICPi-AKI or death within 30 days following completion of CS treatments, including 5 of 56 patients (8.9%) in the shorter treatment duration group and 12 of 109 (11%) in the longer duration group (figure 2A). In

Table 2 Characteristics of initial episode of ICPi-AKI

Variable	Shorter duration (n=56)	Longer duration (n=109)	P value
Time to ICPi-AKI, days, median (IQR)	97 (63–188)	112 (56–224)	0.81
ICPi-AKI stage,* n (%)			0.37
Stage 1	8 (14.3)	11 (10.1)	
Stage 2	20 (35.7)	37 (33.9)	
Stage 3	28 (50.0)	61 (56.0)	
KRT, n (%)	4 (7.1)	5 (4.6)	0.49
Hospitalized for AKI, n (%)	33 (58.9)	63 (57.8)	0.99
Nephrologist involved, n (%)	44 (78.6)	94 (86.2)	0.27
Urine studies			
Blood (≥2+) on UA, n (%)	10 (17.9)	11 (10.1)	0.24
Leukocyte esterase (≥2+) on UA, n (%)	11 (19.6)	18 (16.5)	0.77
Pyuria (≥5 WBCs per hpf on UA), n (%)	25 (44.6)	57 (51.4)	0.44
UPCR ≥0.3 g/g, n (%)	16 (28.6)	34 (31.2)	0.87
Biopsied, n (%)	13 (23.2)	38 (34.9)	0.16
ATIN on kidney biopsy, n (%)	13 (100)	38 (100)	0.99
Time to CS Initiation, days, median (IQR)	3 (0–7)	2 (0–5)	0.43
Initial daily oral CS dose (prednisone equivalent units, mg), median (IQR)	60 (58–60)	60 (60–88)	0.78
Received intravenous pulse CS, n (%)	17 (30.4)	26 (23.9)	0.58
Non-CS immunosuppression,† n (%)	1 (1.8)	2 (1.8)	0.99
Rechallenged, n (%)	13 (23.2)	15 (13.7)	0.13
Recurrent ICPi-AKI after rechallenge, n (%)	1 (1.8)	2 (1.8)	0.99

A total of 28 patients (50%) were missing data on UPCR, and 8 (14.3%) were missing data on leukocyte esterase, blood, and pyuria on UA in the shorter duration group. A total of 52 patients (47.8%) were missing data on UPCR, and 28 (25.7%) were missing data on leukocyte esterase, blood, and pyuria on UA in the longer duration group.
*AKI stages are defined by Kidney Disease: Improving Global Outcomes criteria.
†One patient in the shorter duration group received tocilizumab. In the longer duration group, one patient received mycophenolate mofetil, and one received infliximab.
ATIN, acute tubulointerstitial nephritis; CS, corticosteroid; hpf, high power field; ICPi-AKI, immune checkpoint inhibitor-associated acute kidney injury; KRT, kidney replacement therapy; SCr, serum creatinine; UA, urinalysis; UPCR, urine protein:creatinine ratio; WBCs, white blood cells.

the shorter treatment duration group, 3 of 56 patients developed recurrent ICPi-AKI and 2 of 56 died in the 30 days following completion of treatment with CS. In the longer duration treatment group, 3 of 109 patients developed recurrent ICPi-AKI and 9 died in the 30 days following completion of treatment with CS.

Recurrent ICP-AKI or death occurred at a median of 20 days (IQR, 14–20) and 5 days (IQR, 1–18) in the shorter and longer treatment duration groups, respectively (log-rank p=0.90) (figure 2A). Nadir SCr in the first 14, 28, and 90 days following CS initiation was similar between groups (p=0.40, p=0.56, and p=0.89, respectively) (figure 2B).

When examining the characteristics of the 17 patients who developed recurrent ICPi-AKI or death compared with the 148 who did not, the former tended to be older and to have a lower baseline estimated glomerular filtration rate compared with the latter, but these findings did not reach statistical significance (online supplemental table S3). No characteristic reliably predicted recurrent ICPi-AKI or death (online supplemental table S3).

In a sensitivity analysis limited to patients who were biopsied, none of the 13 patients in the shorter duration group and 4 of the 38 patients (10.5%) in the longer duration group developed recurrent ICPi-AKI or death within 30 days of CS treatment completion (p=0.56).

DISCUSSION

In this international multicenter cohort study of adults with ICPi-AKI, we found no difference in the incidence or timing of recurrent ICPi-AKI or death in patients treated with shorter versus longer durations of CS. These data suggest that shorter durations of CS may be similarly efficacious and safe compared with longer durations.

Guidelines from the National Comprehensive Cancer Network recommend that ICPi-AKI should be treated with CS, gradually tapered over 4–6 weeks and only once the SCr improves to grade 1 toxicity or below.[7] However, data supporting these recommendations are scarce. Lee *et al* examined outcomes among 13 patients with ICPi-AKI treated with a short duration of CS (tapered to ≤10 mg

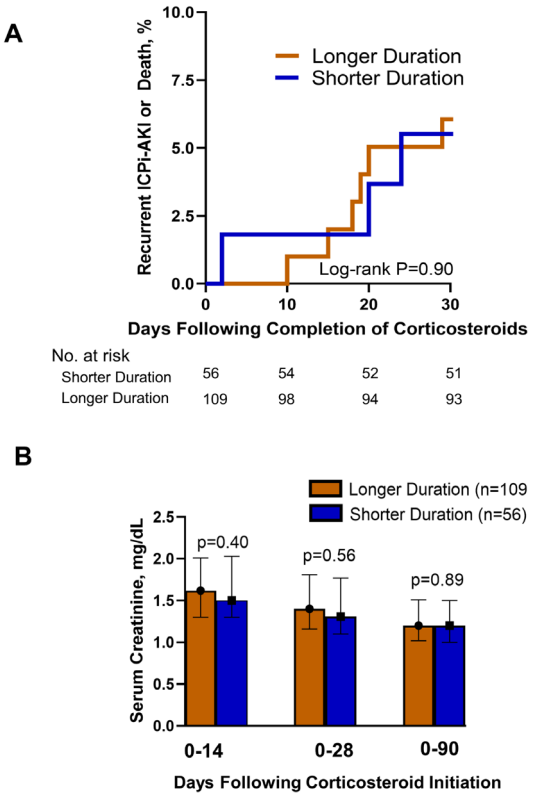

Figure 2 Recurrent ICPi-AKI or death and longitudinal kidney function following completion of shorter versus longer duration of treatment with corticosteroids. (A) Kaplan-Meier curve showing risk of recurrent ICPi-AKI or death in the 30 days following completion of treatment with corticosteroids. N=56 in the shorter duration group; n=109 in the longer duration group. (B) Nadir serum creatinine in the shorter versus longer duration of corticosteroid therapy groups. Median serum creatinine levels are depicted, with error bars representing IQR. ICPi-AKI, immune checkpoint inhibitor-associated acute kidney injury.

daily of prednisone equivalents within 3 weeks) versus 14 patients treated with a longer duration of CS, and found no significant difference in the time to renal recovery between groups.[8] Our data are consistent with these findings and expand on them in a larger and more generalizable cohort.

Data on the impact of CS on cancer outcomes among patients receiving immunotherapy are mixed. Some studies found that administration of CS is not associated with reduced efficacy of immunotherapy,[9 10] while others demonstrated an association with decreased progression-free survival.[11 12] Irrespective of a potential negative effect on the antitumor efficacy of immunotherapy, prolonged use of high-dose CS can cause numerous adverse effects.[4 5] Additionally, longer durations of high-dose CS may preclude early rechallenge with ICPis, which has been shown to be safe in the vast majority of patients with ICPi-AKI.[3]

We acknowledge several limitations. First, we focused on recurrence of ICPi-AKI or death within the first 30 days following completion of CS treatment, and therefore we cannot exclude the possibility that differences between groups may have been observed with longer follow-up. Second, given the relatively small number of events, we could not study the multivariable-adjusted risk of recurrent ICPi-AKI or death, though notably there were no predictors even in univariate analyses (online supplemental table S3). Third, we did not have data on cancer outcomes.

In summary, we found no difference in the risk of recurrent ICPi-AKI or death among patients who received shorter versus longer durations of treatment with CS. Randomized clinical trials are needed to further investigate the effects of varying durations of CS on renal and extrarenal outcomes in patients with ICPi-AKI.

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