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Long-term renal outcomes in ICI-associated acute interstitial nephritis: a comprehensive comparative study

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Background and Aims: Immune checkpoint inhibitors (ICI) have transformed cancer treatment, but they may lead to immune-mediated acute interstitial nephritis (ICI-AIN), in 2-5% of patients. About 35-40% show full kidney function recovery three months post ICI-AIN. Limited evidence exists for long-term renal toxicity. The unknown difference in long-term renal function evolution between partial and complete recovery of the acute episode in ICI-AIN is an unexplored area for future research. Additionally, there's no comparative study on the long-term renal function evolution between ICI-AIN and cases associated with other drugs (Drug-AIN) or autoimmune causes (AI-AIN).

Method: Retrospective, descriptive and observational study. The medical records of all AIN cases diagnosed in the Nephrology Unit of the Bellvitge University Hospital between 2010 and 2023 were reviewed. Longitudinal data on treatments, comorbidities and kidney function were collected. Data was analyzed using descriptive statistics, Chi-square tests, Mann-Whitney U tests and Kaplan Meier analyses.

Results: A total of 94 out of 96 screened patients were diagnosed with AIN (AI-AIN n = 26; Drug-AIN n = 30; ICI-AIN n = 38). Of those, 89.4% were biopsy-confirmed. Median follow-up was 36.64 months (IQR 12.32-74.28). There were not differences in baseline serum creatinine (sCreat) across the groups, defined as sCreat 6 months prior to AIN. At diagnosis, sCreat was lower in ICI-AIN compared to Drug-AIN (267.62 ± 116.44 vs 553.20 ± 317.46, $p < 0.001$), but significant differences were not found comparing to AI-AIN. There were not differences in the cumulative dose and days of treatment with prednisone between the three groups.

In the first year, 35.5% of ICI-AIN patients and 10.3% with Drug-AIN returned to baseline kidney function ($p = 0.020$). Over the course of three years, 45.9% reverted to baseline in the ICI-AIN cohort compared to 18.5% in the Drug-AIN cohort ($p = 0.023$). This trend continued at 5 years, with 45.9% in ICI-AIN and 22.2% in Drug-AIN recovering to baseline ($p = 0.051$). The proportion of patients who recovered baseline kidney function was comparable between the group diagnosed with ICI-AIN and the group diagnosed with AI-AIN at all evaluated time points.

Kaplan-Meier analysis at 1, 3, and 5 years of follow-up revealed a shorter time to sCreat recovery to baseline in the ICI-AIN group compared to the Drug-AIN group, with Log-rank (Mantel-Cox) p-values of 0.016, 0.004, and 0.006, respectively. On the contrary, Kaplan-Meier analysis at the same time points did not reveal differences in time to basal sCreat recovery in ICI-AIN compared to AI-AIN.

Among the evaluated variables, only baseline sCreat influenced the recovery of baseline kidney function in in the univariate analysis, with an odds ratio of 0.95 (95% CI 0.903-1, p-value 0.049) in the ICI-AIN group.

The mean nadir sCreat and estimated glomerular filtration rate (eGFR) after treating AIN were comparable between ICI-AIN and Drug-AIN patients (nadir sCreat: 107.46 µmol/L and 102.24 µmol/L, respectively; nadir eGFR: 61.89 ml/min and 56.96 ml/min, respectively; p-value ns). However, ICI-AIN patients reached nadir renal function more rapidly after treatment initiation (10.99 vs. 28.06 months, p-value = 0.020). After reaching nadir function, 73.7% of ICI-AIN patients showed decline, similar to Drug-AIN (73.3%) and AI-AIN (88.5%, p ns). Yet, ICI-AIN patients had a higher yearly eGFR decline post-nadir compared to Drug-AIN (−17.05 (ml/min)/year vs. −3.99 (ml/min)/year, p-value 0.006) and autoimmune AIN (−4.09 (ml/min)/year, p-value 0.009).

Conclusion: In summary, the results of our study suggest that ICI-AIN patients demonstrate a distinctive pattern of recovery after the acute episode and long-term decline in kidney function after reaching the nadir kidney function compared to the Drug-AIN and AI-AIN groups. They exhibit a faster recovery to nadir kidney function but experience a higher yearly decline post-nadir in eGFR. The influence of baseline sCreat on recovery underscores the importance of considering individual patient characteristics in predicting outcomes and optimizing kidney function before initiating treatment with ICI.