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RESEARCH LETTER

Major Adverse Cardiovascular Events and the Timing and Dose of Corticosteroids in Immune Checkpoint Inhibitor–Associated Myocarditis

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Immune checkpoint inhibitors (ICIs) are being increasingly applied to a broader range of cancers. Myocarditis is an uncommon but potentially fulminant toxicity associated with ICIs, with a case fatality rate of 30% to 50%.[1,2] Corticosteroids are the first-line treatment; however, because of the limited data, guidelines vary significantly in terms of initial corticosteroid dose and treatment strategies.[3,4]

An international multicenter registry of ICI-associated myocarditis from 23 sites was established by retrospectively collecting consecutive patients with ICI-associated myocarditis. The diagnosis was made in 1 of 2 ways: (1) histopathology or (2) clinically suspected myocarditis based on the European Society of Cardiology guidelines.[5] The study was approved by each center's institutional review board. The dose of corticosteroids was converted to methylprednisolone equivalents. Patients were categorized into low-dose (<60 mg/d), intermediate-dose (60–500 mg/d), and high-dose (501–1000 mg/d) groups based on initial methylprednisolone equivalent administered on the first day of treatment. The time of initiation was the time from admission to the first dose of corticosteroids, separated into groups of ≤24 hours, 24 to 72 hours, and >72 hours. Major adverse cardiac events (MACE) were a composite of cardiovascular death, cardiac arrest, cardiogenic shock, and hemodynamically significant complete heart block requiring pacemaker. The beginning of follow-up was the time of index admission for myocarditis, and the end of follow-up was May 1, 2019.

In total, 126 patients were treated with corticosteroids, with 65 diagnosed by histopathology and 61 with clinical criteria. Sixteen of the 126 patients used additional immunosuppressant drugs, with similar characteristics as patients who received corticosteroids only. The median time from ICI administration to the admission was 51 days (interquartile range, 23–120 days). Eighty-four patients (67%) presented with signs or symptoms typical for heart failure, and 39 (31%) presented with arrhythmia. The initial corticosteroid was either methylprednisolone (96 [76%]), prednisone (25 [20%]), hydrocortisone (2 [2%]), or dexamethasone (3 [2%]). Twenty-one patients (16.7%) received low-dose corticosteroids, 55 (43.7%) received intermediate-dose corticosteroids, and 50 (39.6%) received high-dose corticosteroids; groups were broadly similar in characteristics. Patients who received corticosteroids within 24 hours (43 [34.1%]), between 24 and 72 hours (35 [27.8%]), and after 72 hours (43 [38.1%]) also appeared similar in characteristics. Patients who received corticosteroids within 24 hours were less likely to have persistent troponin elevation at discharge (reduction of <50% of the peak troponin levels; 32.4%) than those treated between 24 and 72 hours (66.7%) and after 72 hours (41.4%; P=0.026). There was an inverse relationship between initial dose of corticosteroids and the occurrence of MACE (low dose, 61.9%; intermediate dose, 54.6%; high dose, 22.0%; P<0.001; Figure [A]). Compared with low-dose corticosteroids, high dose was associated with a 73% lower risk of

The full author list is available on page 2033.

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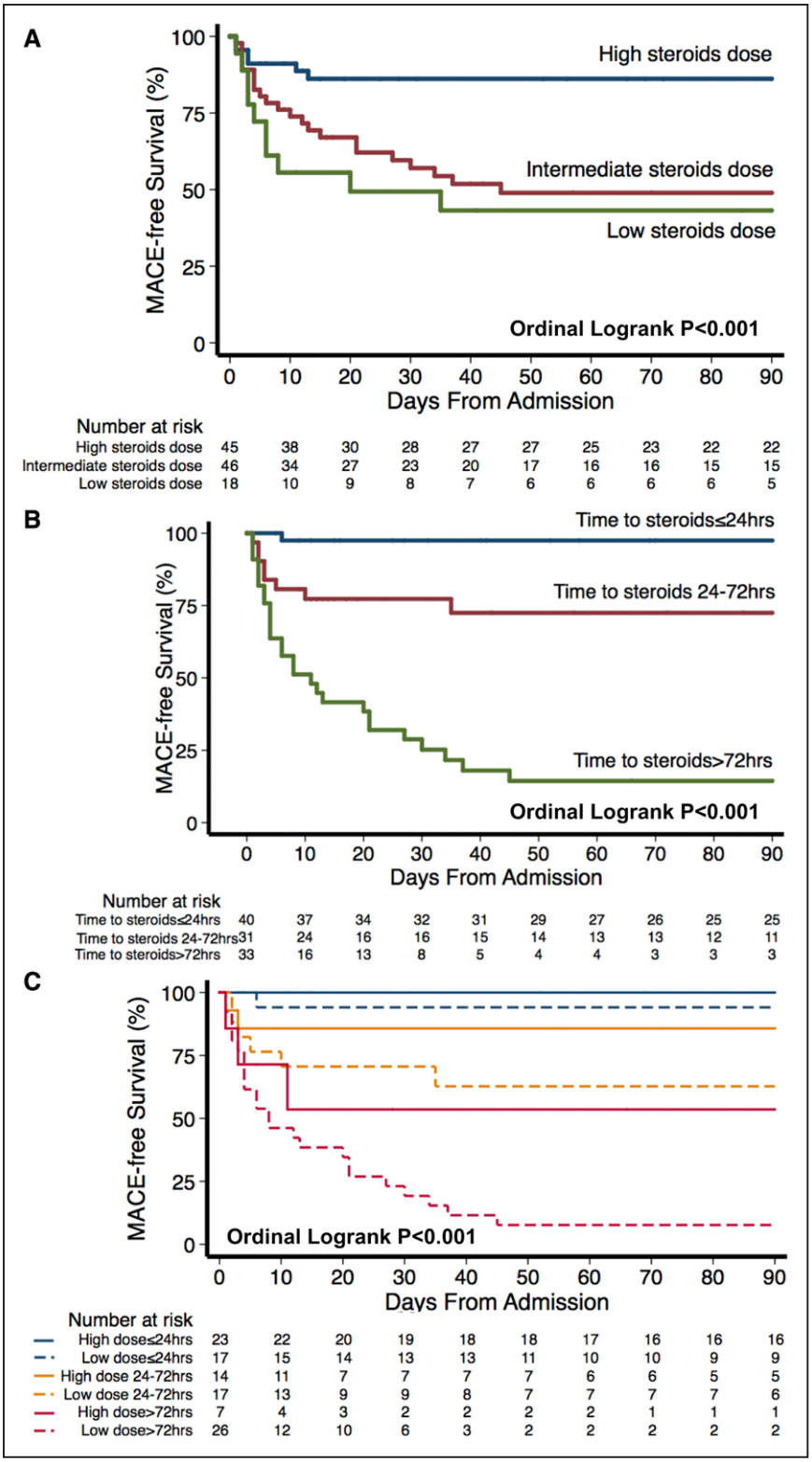

Figure. Relationship between initial corticosteroids dose and timing and MACE-free survival.
Kaplan-Meier curves by initial corticosteroids dose (**A**), by time of initiation (**B**), and by initial dose of corticosteroids and time of initiation combination (**C**). MACE indicates major adverse cardiovascular events.

MACE independent of age, sex, lowest left ventricular ejection fraction, and time of initiation (hazard ratio, 0.27 [95% CI, 0.09–0.84]; *P*=0.024). Patients receiving corticosteroids within 24 hours of admission also had a lower rate of MACE (7.0%) than those receiving corticosteroids between 24 and 72 hours (34.3%) and those receiving corticosteroids at >72 hours (85.1%; *P*<0.001; Figure [B]). Compared with after 72 hours, initiation of corticosteroids within 24 hours of admission (hazard ratio, 0.03 [95% CI, 0.004–0.23]; *P*=0.001) and between 24 and 72 hours (hazard ratio, 0.30 [95% CI, 0.12–0.73]; *P*=0.008) was associated with a lower

risk of MACE after adjustment for age, sex, lowest left ventricular ejection fraction, and initial corticosteroid dose. Patients were further categorized into time and dose combination groups, by dividing the cohort into ≤24 hours, 24 to 72 hours, and >72 hours and high-dose (methylprednisolone 1000 mg/d) and non–high-dose corticosteroids (any dose <1000 mg/d) groups. The time of initiation impacted MACE-free survival, whereby patients receiving corticosteroids within 24 hours, regardless of dosage (blue curves), showed the best outcome, and patients receiving corticosteroids after 72 hours, regardless of dosage (red curves), showed the worst outcome (Figure [C]).

These results raise the possibility that myocardial damage can be mitigated by early and intensive corticosteroid therapy.[3,4] There appeared to be a graded reduction in the risk of MACE as the time of initiation became shorter and initial dose became higher. The initiation time of corticosteroids appeared to play a stronger role, such that using high-dose corticosteroids could not overcome the effect of corticosteroids given later. In contrast, non–high-dose corticosteroids administered within 24 hours may lead to a better outcome as compared to patients who receive high-dose corticosteroids later (24–72 or >72 hours).

This was a retrospective observational study; therefore, the association of corticosteroid dosing and time is hypothesis generating, and future randomized, controlled trials will be needed to provide more definitive evidence and closely monitor cancer outcomes. Specifically, the effect of high-dose corticosteroids on cancer outcomes with ICIs is unclear; initial data suggested that cancer outcomes were unchanged by high-dose corticosteroids, but more recent data suggest that cancer survival may be reduced. Therefore, there is likely a pressing need for therapies beyond corticosteroids that will not affect cancer outcomes.

In conclusion, higher initial dose (ie, intravenous methylprednisolone 1000 mg/d) and earlier initiation of corticosteroids in a retrospective study were associated with improved cardiac outcomes with ICI-associated myocarditis.

ARTICLE INFORMATION

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