**Major Adverse Cardiovascular Events and the Timing and Dose of Corticosteroids in Immune Checkpoint Inhibitor-associated Myocarditis**

Zhang and Corticosteroids in ICI myocarditis

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Immune checkpoint inhibitors (ICI) are being increasingly applied to a broader range of cancers. Myocarditis is an uncommon, but potentially fulminant toxicity associated with ICI, with a case fatality rate of 30-50%.1, 2 Corticosteroids are the first-line treatment; however, due to the limited data, guidelines vary significantly in terms of initial corticosteroids 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 one of two 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 (<60mg/day), intermediate (60-500mg/day) and high (501-1000mg/day) dose 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 and was separated into ≤24 hours, 24-72 hours and >72 hours groups. 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 on May 1st, 2019.

In total, 126 patients were treated with corticosteroids, with 65 diagnosed with histopathology and 61 using clinical criteria. Sixteen of the 126 patients used additional immunosuppressants, 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, 50 (39.6%) received high-dose; groups were broadly similar in characteristics. Patients who received corticosteroids within 24 hours (43, 34.1%), between 24-72 (35, 27.8%) and after 72 hours (43, 38.1%) also appeared similar. 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%), compared with those treated between 24-72 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, 54.6%, high-dose 22.0%, P<0.001, Figure 1A, P=0.001). Compared with low-dose corticosteroids, high-dose was associated with a 73% lower risk of MACE independent of age, sex, lowest LVEF and time of initiation (HR=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%) compared with those between 24-72 hours (34.3%) and those >72 hours (85.1%, P<0.001, Figure 1B, P<0.001). Compared with after 72 hours, initiating corticosteroids within 24 hours of admission (HR=0.03, 95% CI 0.004, 0.23, P=0.001) and between 24-72 hours (HR=0.30, 95% CI 0.12, 0.73, P=0.008) was associated with a lower risk of MACE after adjusting for age, sex, lowest LVEF and initial corticosteroid dose. Patients were further categorized into time and dose combination groups, by dividing the cohort into ≤24 hours, 24-72 hours and >72 hours and high-dose (methylprednisolone 1000mg/day) and non-high dose corticosteroids (any dose <1000mg/day) 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 1C).

 These results raise the possibility that myocardial damage can be mitigated by early and intensive corticosteroids 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 ≤24 hours may lead to a better outcome compared with patients who received high-dose later (24-72 or >72 hours).

This was a retrospective observational study; therefore, the association of corticosteroids dosing and time is hypothesis-generating and future randomized controlled trials will be needed to provide more definitive evidence and closely follow cancer outcomes. Specifically, the effect of high-dose steroids on cancer outcomes with ICI’s 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 which will not affect cancer outcomes.

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

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**Figure legends:**

Figure 1. Kaplan-Meier curves by initial corticosteroids dose (A), time of initiation (B) and by corticosteroids initial dose and time of initiation combination (C).