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Systemic corticosteroid therapy may delay viral clearance in patients with Middle East Respiratory Syndrome Coronavirus infection

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Middle East respiratory syndrome (MERS) is caused by a novel single-stranded, positive-sense RNA beta-coronavirus (CoV) and the case fatality rate of MERS-CoV infection is much higher than that due to severe acute respiratory syndrome (SARS)-CoV.[1] MERS-CoV causes aberrant induction of inflammatory cytokines and chemokines that could be important in the disease pathogenesis.[2] Autopsy of a fatal case has revealed evidence of diffuse alveolar damage, necrotizing pneumonia, acute renal injury, lobular and portal hepatitis, and myositis with infiltration by macrophages.[3] A retrospective cohort study of 330 critically ill patients with MERS-CoV infection in Saudi Arabia has shown that on admission to intensive care unit (ICU), patients with severe acute respiratory infection (SARI) due to MERS-CoV had more severe hypoxemia and more extensive radiographic pulmonary infiltrates compared to other patients with non-MERS SARI. In addition, more MERS SARI patients required invasive mechanical ventilation and other types of respiratory support compared to those with non-MERS SARI.[4] As there is no specific antiviral therapy proven to be effective for treatment of MERS-CoV infection, systemic corticosteroid has been used in over 50% of critically ill patients with MERS-CoV infection in an attempt to modulate cytokine dysregulation but the impact on clinical outcome is uncertain.[4]

Arabi et al [5] have recently conducted a retrospective study examining the effects of systemic corticosteroid therapy on 90-day mortality and MERS-CoV RNA clearance based on the same cohort data involving 14 ICUs in Saudi Arabia.[4] The authors have adjusted for baseline and time-varying confounders (such as worsening clinical status and the decision timing to start corticosteroid therapy) using marginal structural models and found no difference of the effect of systemic corticosteroid on 90-day mortality. The study was limited by the retrospective

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observational design and lack of a standardized protocol for rRT-PCR testing and corticosteroid treatment regime with some missing data. Nevertheless, the investigators had performed marginal structural Cox proportional hazards model and sensitivity analyses to minimize the impact of these limitations and shown that corticosteroid therapy was associated with a longer duration of about 7 days to viral clearance.[5]

Systemic corticosteroid has been widely used in managing patients with SARI of viral etiology but there are mainly observational data examining its impact on clinical outcome. During the major outbreak of SARS-CoV infection in 2003, a randomized controlled trial (RCT) showed that early use of hydrocortisone was associated with a higher plasma SARS-CoV viral load with delayed viral clearance compared to a control group that received normal saline.[6] A meta-analysis of data focussing on treatment of patients with severe influenza A(H1N1)pdm09 has shown that systemic corticosteroid was associated with an increase in mortality (OR 3.06, 95%CI 1.58 to 5.92).[7] In patients hospitalized with influenza A (H7N9) viral pneumonia in China, an observational study has shown that high-dose corticosteroid (defined as > 150 mg/d methylprednisolone eqv) was associated with increased risks in 30 day mortality (38.5% vs 7.7%, p=0.021) and 60 day mortality (50% vs 15.4%, p=0.022) and longer viral shedding (15 vs 13 days, p=0.039) while there was no difference between low dose (25–150mg/d methylprednisolone) and controls.[8] Another observational study of patients hospitalized with influenza A(H1N1)pdm09 infection in China has shown that corticosteroid therapy overall did not influence either 30-day or 60-day mortality. However, in a subgroup analysis among patients with PaO_2/FiO_2<300mmHg, low-to-moderate dose of corticosteroid treatment (equivalent to 25-150mg/day of methylprednisolone) significantly decreased both 30-day

mortality (aHR 0.49 [95% CI 0.32-0.77]) and 60-day mortality (aHR 0.51 [95% CI 0.33-0.78]), while high-dose (>150mg/day) of corticosteroids therapy yielded no difference.[9] In an observational study of 2649 adults hospitalized with seasonal influenza and influenza A(H1N1)pdm09 infection in Hong Kong, Singapore and Beijing in 2008-2011, 23.1% of patients had received systemic corticosteroid, which increased the risks of super-infections (from 2.7% to 9.7%) and deaths when controlled for its indications (adj HR 1.7, 95% CI 1.1–2.6).[10] However analyses of these observational data usually do not take into consideration time-varying confounders, as Arabi et al[5] did, and may generate potentially biased estimates of treatment effect.

Nosocomial outbreaks are a hallmark of MERS-CoV infection and account for about 40% of the total number of human infections.[1] It is important to note that MERS-CoV concentrations peak in the respiratory tract of the patients during the second week of illness,[11] while the patients may transmit MERS-CoV to others from Day 1 to 11 of their illness (median, 7 days; IQR, 5 to 8 days).[12] The interesting study by Arabi et al[5] has been the first publication to shed some light that systemic corticosteroid might delay viral clearance in patients with MERS-CoV infection. From the infection control and prevention point of view, it would be of great interest to see in future studies if systemic corticosteroid therapy would increase the infectivity of patients hospitalized with MERS-CoV infection through prolongation of viral shedding. In addition, Arabi et al[5] did not examine other outcome measures such as opportunistic infections, neuro-myopathy and hyperglycemia but these are important complications to watch out for with corticosteroid therapy in future studies.

Currently the main treatment of MER-CoV infection remains supportive therapy.[1,13] Based on

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data from the marmoset model, interferon and lopinavir appear to have good inhibitory effects against MERS-CoV.[14] Monoclonal and polyclonal antibodies which inhibit the spike protein of MERS-CoV are potentially useful treatment modalities that are undergoing clinical trials in the Middle East.[13] Retrieval of convalescent plasma from patients who have recovered from MERS-CoV infection as passive immunotherapy is difficult as the antibody responses in survivors who had severe disease lasted for less than 1 year whereas those with milder disease could not maintain antibody response soon after recovery from the acute illness.[15] The results of the current observational study,[5] together with data from treatment of SARS-CoV infection,[6] seasonal and avian influenza,[7-12] suggest that the risk of systemic corticosteroid would likely exceed any benefit for treatment of MERS-CoV infection.[13] More clinical studies preferably with a RCT design with a standardized treatment and serial viral sampling protocol are needed to evaluate more scientifically the role of interferon, lopinavir, passive immunotherapy such as monoclonal/ polyclonal antibodies, and systemic corticosteroid in the clinical management of MERS-CoV infection.

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