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Methylprednisolone Pulses as an Effective Treatment in Multisystem Inflammatory Syndrome in Children Associated with SARS-CoV-2 (MIS-C), and the Best Alternative for IVIG

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Dear Editor,

Multisystem Inflammatory Syndrome in Children associated with SARS-CoV-2 (MIS-C) has been described as a cytokine storm similar to Kawasaki disease shock syndrome (KDSS), secondary hemophagocytic lymphohistiocytosis (HLH), and toxic shock syndrome (TSS), resulting in multi-organ failure (1). However, decisions about treatment have been challenging due to the unknown exact pathophysiological pathway. Methylprednisolone pulses (MPP) as initial treatment in MIS-C have not been clearly prescribed, similar to secondary HLH or KDSS. In a study by the Swissped RECOVERY Trial Group in February 2023, MPP in lower doses (10 mg/kg) in combination with IVIG (2 g/kg) was preferred. However, respiratory support in the MPP group was less than in the IVIG group, and there was no significant difference in the duration of hospital stay between the two groups. They reported no significant differences in the need for and duration of inotropes, cardiac events, and other complications (2).

At Tehran Children Medical Center, a pediatric center of excellence in Iran, based on the pathophysiology of KDSS (with coronary and myocardial involvement) and macrophage activation syndrome (MAS) as secondary HLH, MPP was initiated as the first-line treatment according to an algorithm (3). This algorithm was designed by the Pediatric Rheumatology and other related departments based on their experiences in treating MAS with MPP and evidence of elevated levels of ferritin in MIS-C, similar to MAS, as an indicator of macrophage activation. Due to limitations in accessing IVIG during the COVID pandemic in Iran, MPP was preferred.

Based on this experience, outcomes of patients treated with MPP therapy were reported in December 2022. About 29% of patients required ICU admission, and there was a significant correlation between the delay in MPP initiation and ICU admission. Laboratory data on hyperinflammation such as ferritin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), alanine transaminase (ALT), and aspartate transaminase (AST) showed significant differences before and after MPP treatment (4).

Recently, in a randomized, controlled, open-label platform trial published by the RECOVERY Collaborative Group in January 2024, authors reported that MPP reduced the duration of hospital stay in children with MIS-C. Tocilizumab was shown to be effective as a second-line treatment for children with refractory responses. IVIG and anakinra did not affect hospital stay in this study (5).

Nowadays, the role of the Interferon signature in pediatric multisystem inflammatory syndrome has been highlighted as being protective against severe COVID infection or adult hyperinflammatory syndrome (6). In the acute phase of Kawasaki disease, especially in KDSS with myocarditis, the cytokine storm plays a pivotal role in myocardial dysfunction through macrophage activation. Interferon, as one of the initial important

cytokines inducing cytokine storms, plays a pivotal role in macrophage and neutrophil activation, leading to interleukin 6 (IL6) production and STAT pathway activation. Limiting the activation of neutrophils and macrophages by MPP, similar to MAS or IL6 inhibition, may be beneficial in mitigating the cytokine cascade (7).

In the cytokine storm of MIS-C, treatment should be proactive to prevent complications, and prompt decision-making for aggressive treatment could help prevent complications. Methylprednisolone pulses appears to be the most effective treatment currently available. However, long-term follow-up is needed to compare long-term complications associated with different treatments.

Footnotes

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