EDITORIALS

Immunotherapy for MIS-C — IVIG, Glucocorticoids, and Biologics

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Since the sudden emergence of multisystem inflammatory disease in children (MIS-C) in April 2020 as a novel and severe presentation of coronavirus disease 2019 (Covid-19), nearly 4000 cases of MIS-C and 35 deaths have been reported in the United States and many more internationally.[1-4] A steep learning curve for the identification, diagnosis, and treatment of this condition has been effective through rapid communication globally among multidisciplinary specialists at pediatric centers who faced the challenge of caring for the affected children. In a triumph of collaboration, experts achieved consensus about diagnostic criteria and the need to induce rapid immunomodulation aimed at limiting the course of the illness. However, in the absence of randomized, controlled clinical trials, consensus around specific immunomodulatory therapies has been more elusive, given the speed with which centers have had to establish cohorts and deliver treatment. Therapies have included intravenous immune globulin (IVIG), glucocorticoids, and biologic agents in various combinations, depending on the treating center.[5-9]

Two groups now report in the *Journal* early outcomes of large observational trials — results that superficially seem to have conflicting findings regarding the efficacy of immunomodulation with IVIG, glucocorticoids, or both. The Overcoming Covid consortium[10] (consisting of investigators at 58 U.S. hospitals reporting on 518 patients from March through October 2020) determined that initial MIS-C treatment with IVIG plus glucocorticoids was associated with a lower risk of cardiovascular dysfunction and the initiation of vasopressors and adjunctive therapy than treatment with IVIG alone. In contrast, the international Best Available Treatment Study (BATS) consortium[11] (consisting of investigators in 32 countries reporting on 614 patients from June 2020 through February 2021) found no statistically significant differences in odds ratios for end points of ventilation, inotropic support, or death or for improvement on an ordinal clinical-severity scale for any of three treatments: IVIG alone, a combination of IVIG and glucocorticoids, or glucocorticoids alone. The risk of escalation of immunomodulatory treatment in patients who received IVIG plus glucocorticoids was significantly lower than the risk in patients who received IVIG alone, a finding that was in line with the results of the U.S. study. However, this effect was not observed in a comparison of glucocorticoid monotherapy with IVIG monotherapy. The effects on the secondary outcome of the time until a reduction in organ failure and inflammation was similar across all three treatments.

What are possible reasons for these apparently disparate results and what do they mean for clinicians who are treating a critically ill child with MIS-C? First, the consortia represent different patient populations. The Overcoming Covid consortium included only U.S. patients, whereas the BATS consortium encompassed international hospitals, including at least one large U.S. center. It is possible that differences in genetic background, which could be associated with a dysregulated immune response in patients with MIS-C, led to different responses to specific types of immunomodulation.

Second, the time periods for which the investigators were evaluating surveillance data in these studies differed in two important ways. The U.S. study included only patients who had been hospitalized during the earlier and smaller waves of the Covid-19 pandemic, before any substantial

circulation of variants. The BATS investigators were reviewing cases both before and after the emergence of Covid-19 variants in many countries, and they were analyzing data for patients who had presented during the first, second, and massive third wave of Covid-19 circulation. It is possible that the dysregulated hyperimmune response of MIS-C could vary or change according to the strain of initial infection, reexposure to differing or mismatched variants, or prolonged and repetitive exposure over longer periods of virus circulation within a community.

Third, although large consortium trials improve the statistical power to evaluate the effect of therapies for rare diseases and are potentially more broadly generalizable, they cannot replace well-characterized, large prospective cohorts at single centers using a standardized approach to treatment.[12] Whereas researchers in the two trials used statistical methods such as propensity-score adjustment to control for confounding factors that might have influenced treatment and for variations in care at multiple centers, these modeling approaches cannot fully compensate for such variations. Among the most important of these variations are the criteria used for initiating immunomodulatory treatments, which could potentially lead to unavoidable differences in the interpretation of efficacy.

Fourth, although it is becoming increasingly clear that swift and decisive institution of immunomodulatory therapy can be lifesaving in patients with MIS-C, neither of these studies definitively answered the question about the most effective single or combination treatment. Specifically, neither study was powered to include an evaluation of approaches that steer away from broad immunosuppression with glucocorticoids and that focus on more targeted and titratable treatments with biologic agents, such as anakinra and infliximab. In this regard, clinicians must avoid the pitfall of interpreting a lack of data as a lack of efficacy. Randomized, controlled trials to evaluate the safety and efficacy of regimens comparing biologic agents with glucocorticoids (with or without IVIG) have not yet been performed.

Finally, it must be appreciated that neither of these groups of investigators has yet assessed the effect of therapies on long-term outcomes — specifically, the comparative efficacy for progression or resolution of coronary abnormalities, prolonged or permanent cardiac dysfunction, or scarring. Systematic and comprehensive long-term follow-up for these and other noncardiac outcomes — including sequelae involving pulmonary issues, mental health, neurodevelopment, and quality of life — are sorely needed in the pediatric population and will launch soon. Meanwhile, continued collaboration across centers is essential to decreasing the short-term incidence of death and complications, particularly as Covid-19 continues to circulate internationally, and to evaluating the effect of vaccination in younger age groups.

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