Remestemcel-L Therapy for COVID-19–Associated Multisystem Inflammatory Syndrome in Children

Allison Ross Eckard, MD,a Kenneth M. Borow, MD,b Elizabeth H. Mack, MD,a Elizabeth Burke, MS, ANPC,c Andrew M. Atz, MDa

Abstract

Multisystem inflammatory syndrome in children (MIS-C) is a serious postinfectious immune dysregulation associated with coronavirus disease 2019 that may present with severe and life-threatening cardiovascular dysfunction, hemodynamic instability, shock, and multisystem organ failure. Optimal treatment is unknown. Current standard of care consists of nonspecific anti-inflammatory and antithrombotic therapies. Interventions that target MIS-C’s distinctive clinical features and immunophenotype are indicated. Remestemcel-L, an investigational mesenchymal stromal cell therapy, is a promising candidate for treatment of MIS-C because of its beneficial anti-inflammatory, immunomodulatory, endothelial function and vascular stabilizing effects, which align well with the pathophysiology of MIS-C. Here, we present the first two patients with life-threatening MIS-C ever treated with remestemcel-L under an expanded access program. Both were previously healthy children without any indication of previous coronavirus disease 2019 infection or exposure. They presented with severe clinical illness including myocardial dysfunction, hemodynamic instability, hypotension, acute kidney injury, and shock. At the time of hospital admission, both had negative polymerase chain reaction (PCR) test results and positive serology results for severe acute respiratory syndrome coronavirus 2. Both children received standard of care MIS-C treatment. Although the patients showed some clinical improvement, left ventricular ejection fraction remained reduced and inflammatory biomarkers remained significantly elevated. When treated with two intravenous doses of remestemcel-L separated by 48 hours, rapid normalization of left ventricular ejection fraction, notable reductions in biomarkers of systemic and cardiac inflammation, and improved clinical status occurred. Neither child experienced adverse effects associated with remestemcel-L administration. This treatment appears promising as a novel immunomodulatory cellular therapy for children with clinically significant cardiovascular manifestations of MIS-C.

The global coronavirus disease 2019 (COVID-19) pandemic, caused by the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused devastating worldwide morbidity and mortality.¹,² Many adults, particularly those with underlying conditions and/or advanced age, are at high risk of life-threatening disease. In contrast, children rarely develop severe illness or die of COVID-19.³ One exception is multisystem inflammatory syndrome in children (MIS-C), a rare but serious complication...
of SARS-CoV-2. Many children with MIS-C develop severe or life-threatening illness, often characterized by overwhelming systemic inflammation, coagulopathy, myocardial dysfunction, shock, and multisystem organ failure.4–7

**CLINICAL FEATURES AND PATHOPHYSIOLOGY OF MIS-C**

Pathophysiology of MIS-C is thought to be a postinfectious immune dysregulation caused by SARS-CoV-2. Every organ system in the body can be affected. Common clinical presentations include persistent fever; rash, conjunctivitis, myalgias, gastrointestinal manifestations, and neurocognitive symptoms.4–7 Clinical findings may include shock, myocardial dysfunction, arrhythmias, acute respiratory failure, and acute kidney injury. Laboratory abnormalities often reveal lymphocytopenia, neutrophilia, elevated inflammatory markers (eg, C-reactive protein, D-dimer), and elevated cardiac markers (eg, troponin, B-type natriuretic protein).

Whereas the syndrome shares characteristics with Kawasaki disease (KD) and macrophage activation syndrome, MIS-C has a unique immunophenotype and is considered a discrete disease.8 One important distinction is the high frequency of cardiovascular involvement, especially myocardial and endothelial dysfunction (eg, decreased left ventricular [LV] function, hypotension, and activation of coagulation cascades).6,7,9 The high frequency of distinctive and often severe cardiovascular manifestations in MIS-C raises the need for more targeted treatments beyond the traditional therapies used in KD (eg, intravenous immunoglobulin [IVIg], aspirin, steroids).10

**RATIONALE FOR ADMINISTRATION OF REMESTEMCEL-L IN MIS-C**

Remestemcel-L is an investigational therapy composed of culture-expanded allogeneic mesenchymal stromal cells (MSCs) derived from bone marrow of unrelated adult donors. These cells, part of the mesenchymal lineage cell line, have important properties that align well with the pathophysiology of MIS-C, including beneficial anti-inflammatory, immunomodulatory, endothelial function, and vascular stabilizing effects. The biological basis for mesenchymal lineage cells’ salutary effects involves the secretion of multiple paracrine factors, such as anti-inflammatory cytokines that reduce inflammation, growth factors that can enhance tissue repair, and angiogenic growth factors that improve endothelial function in both coronary and peripheral arteries.11–20

The pattern of anti-inflammatory mediators released by MSCs is in specific response to the inflammatory environment encountered and is likely mediated through differential activation of damage- and pathogen-associated molecular pathogen receptors expressed on their cell surfaces, including toll-like receptors.21,22 Thus, MSCs have more precise immunomodulatory targets than nonspecific therapies like IVIg and steroids. Yet, unlike single pathway-targeted therapies such as interleukin 1 or interleukin 6 inhibitors, MSCs have a wider set of beneficial effects that align well with the pathologic derangements associated with MIS-C.

MSCs have been evaluated for treatment in a variety of immune-mediated and inflammatory conditions. To date, ~1100 people, including 311 children, have received investigational remestemcel-L. Collectively, the data suggest that remestemcel-L has a favorable efficacy and safety profile, including among children with steroid-resistant acute graft-versus-host disease.23,24 Thus, on the basis of MSC’s anti-inflammatory, immunomodulatory, and beneficial effects on endothelial function, as well as remestemcel-L’s safety data in children, this therapy holds promise as an effective and novel treatment of MIS-C.

**CLINICAL SUMMARY**

Here, we present the first two patients with MIS-C ever treated with remestemcel-L under an intermediate-size expanded access program (ClinicalTrials.gov identifier NCT04456439). Legal guardians provided written permission to share their children’s health information.

Both patients (patient 1: a 4-year-old non-Hispanic Black boy; patient 2: a 10-year-old non-Hispanic Black girl) presented to the Medical University of South Carolina (MUSC), Charleston, SC, during August to September 2020 and met the Centers for Disease Control and Prevention definition of MIS-C.4 Detailed clinical data are depicted in Figs 1 and 2. The two patients had strikingly similar presentations: both were previously healthy children who experienced a preceding illness of ~5 days’ duration consisting of high fever (39.0–40.6°C), gastrointestinal symptoms, and generalized malaise. Patient 1 presented to an outside hospital emergency department 3 times during the first 4 days of illness and was sent home with a “viral syndrome” diagnosis each time. Patient 2 was admitted to an outside hospital PICU for 3 days with acute renal insufficiency before transfer.

When both children presented to our institution, they had severe clinical illness, including hemodynamic instability, hypotension, acute kidney injury, and shock requiring vasopressors. Both children had significant myocardial dysfunction, characterized primarily by decreased biventricular function (requiring inotropes in patient 2). Cardiac injury and/or congestion and systemic inflammation and/or coagulation biomarkers were markedly elevated. Patient 2 also had mental status...
<table>
<thead>
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<th>Days since symptom onset</th>
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<th>Outpatient</th>
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<td>Prednisone</td>
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<td>LMWH</td>
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<tr>
<td>High-dose aspirin</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Low-dose aspirin</td>
<td>–</td>
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**Key echocardiogram findings**

<table>
<thead>
<tr>
<th>LV ejection fraction, %</th>
<th>57.6</th>
<th>42.3</th>
<th>51.2</th>
<th>64.1</th>
<th>67.8</th>
<th>59.2</th>
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<td>LV end systolic vol, mL</td>
<td>–</td>
<td>19.6</td>
<td>37.7</td>
<td>37.8</td>
<td>20.3</td>
<td>19.6</td>
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<tr>
<td>LV end diastolic vol, mL</td>
<td>–</td>
<td>46.4</td>
<td>68.3</td>
<td>75.9</td>
<td>56.5</td>
<td>60.9</td>
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</table>

**Main clinical findings**

- Hypotension, tachycardia, epinephrine or norepinephrine
- Intermittent bradycardia, hypertension
- Anemia, PRBCs
- Tachypnea (remained in room air; SpO2 96%–100%)
- Clinically well

**Key blood laboratory findings**

- Total WBC, 10^9/mm^3: 32.9, 42.6, 38.7, 22.2, 18.8, 21.0, 23.5, 18.5, 26.8
- Neutrophils, 10^9/mm^3: 19.6, 40.1, 35.6, 16.2, 14.8, 11.8, 12.0, 12.6, 19.8
- Lymphocytes, 10^9/mm^3: 1.65, 0.83, 2.49, 3.77, 1.15, 5.88, 8.45, 4.44, 2.95
- Platelet count, 10^9/mm^3: 102, 108, 112, 79, 152, 163, 201, 227, 274
- Hemoglobin, g/dL: 12.1, 8.1, 7.6, 9.0, 9.6, 9.5, 7.9, 5.2, 8.7
- C-reactive protein, mg/L: 571, 415, –, 147, 87, 62, 37, 31, 14
- ESR, mm/h: >100, 81, –, –, –, –, –, –, –
- Procalcitonin, ng/mL: >100, –, –, –, 14.8, –, –, 2.9, –
- D-dimer, mg/mL: 12.2, 16.7, 15.9, >20, >20, >20, 17.0, 8.5, 2.6
- Fibrinogen, mg/dL: 831, 807, 588, 392, 230, 167, 149, 144, 154
- Ferritin, mg/mL: 417, 369, 533, 244, 274, 252, 202, 299, 258
- LDH, U/L: 1230, 408, –, –, 395, –, –, 243, –
- Troponin-I, ng/mL: 0.02, 0.01, 0.02, 0.01, –, –, –, –, –
- BNP, pg/mL: 1057, 1339, 3a91, 4665, 785, 153, 240, 47.4, –
- Creatinine, mg/dL: 4.5, 1.4, 0.5, 0.5, 0.4, 0.3, 0.3, 0.3, 0.3
- Urea nitrogen, mg/dL: 83, 54, 22, 30, 31, 28, 19, 24, 16
- AST, U/L: 169, 177, 57, 38, 29, 25, 28, 29, –
- ALT, U/L: 66, 77, 45, 36, 29, 25, 24, –, –
- Clinically well

**FIGURE 1**

Detailed clinical course for patient 1. a First remestemcel-L infusion. b Second remestemcel-L infusion. c Laboratory and echocardiogram data obtained on MSC treatment days 26 and 33, respectively. d Conversion to SI units follows in parentheses for each laboratory measurement: total WBC, neutrophils, lymphocytes, and platelet count to cells × 10^9/L (0.001); hemoglobin to millimoles per liter (0.6206); D-dimer to milligrams per liter (1.0); fibrinogen to grams per liter (0.01); ferritin, procalcitonin, and troponin-I to micrograms per liter (1.0); LDH, AST, and ALT to microkatalis per liter (0.01667); creatinine to micromoles per liter (88.4); urea nitrogen to millimoles per liter (0.3571); and BNP to nanograms per liter (1.0). Laboratory and echocardiogram numbers with bolded font represent abnormal values deemed clinically relevant. ALT, alanine aminotransferase; AST, aspartate aminotransferase; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; LMWH, low-molecular-weight heparin; OSH, outside hospital; PRBC, packed red blood cell; SpO2, pulse oxygen saturation; WBC, white blood cell count.
FIGURE 2
Clinical course for patient 2. a First remestemcel-L infusion. b Second remestemcel-L infusion. c Laboratory and echocardiogram data obtained on MSC treatment days 26 and 33, respectively. d Conversion to SI units follows in parentheses for each laboratory measurement: total WBC, neutrophils, lymphocytes, and platelet count to cells x 10^9/L (0.001); hemoglobin to millimoles per liter (0.6206); D-dimer to milligrams per liter (1.0); fibrinogen to grams per liter (0.01); ferritin, procalcitonin, and troponin-I to micrograms per liter (1.0); LDH, AST, and ALT to microkatals per liter (0.01667); creatinine to micromoles per liter (88.4); urea nitrogen to millimoles per liter (0.3571); and BNP to nanograms per liter (1.0). NB laboratory and echocardiogram numbers with bolded font represent abnormal values deemed clinically relevant. ALT, alanine aminotransferase; AST, aspartate aminotransferase; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; LMWH, low-molecular-weight heparin; OSH, outside hospital; PRBC, packed red blood cell; SpO2, pulse oxygen saturation; WBC, white blood cell count.

### Key blood laboratory findings

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OSH admission</th>
<th>Transfer to MUSC</th>
<th>Hospital discharge</th>
<th>Outpatient</th>
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<tr>
<td>Total WBC, 10^9/mm^3</td>
<td>31.1</td>
<td>16.1</td>
<td>17.7</td>
<td>18.1</td>
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<tr>
<td>Neutrophils, 10^9/mm^3</td>
<td>26.5</td>
<td>14.8</td>
<td>15.9</td>
<td>14.4</td>
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<tr>
<td>Lymphocytes, 10^9/mm^3</td>
<td>1.56</td>
<td>0.853</td>
<td>0.85</td>
<td>0.81</td>
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<td>Platelet count, 10^9/mm^3</td>
<td>197</td>
<td>249</td>
<td>170</td>
<td>193</td>
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<tr>
<td>Hemoglobin, g/dL</td>
<td>11.1</td>
<td>9.3</td>
<td>8.1</td>
<td>8.7</td>
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<td>C-reactive protein, mg/L</td>
<td>158</td>
<td>231</td>
<td>137</td>
<td>72</td>
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<tr>
<td>ESR, mm/h</td>
<td>&gt;100</td>
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</tr>
<tr>
<td>Procalcitonin, ng/mL</td>
<td>29.2</td>
<td>31.6</td>
<td>10.1</td>
<td>7.3</td>
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<tr>
<td>D-dimer, mg/mL</td>
<td>3.1</td>
<td>3.7</td>
<td>2.5</td>
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<td>Fibrinogen, mg/dL</td>
<td>876</td>
<td>891</td>
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<td>Ferritin, ng/mL</td>
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<td>1766</td>
<td>1251</td>
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<td>LDH, U/L</td>
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<tr>
<td>Troponin-I, ng/mL</td>
<td>20.0</td>
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<td>9.7</td>
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<tr>
<td>Urea nitrogen, mg/dL</td>
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<td>1.8</td>
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<td>AST, U/L</td>
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<tr>
<td>ALT, U/L</td>
<td>72</td>
<td>47</td>
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</tbody>
</table>

### Key echocardiogram findings

- LV ejection fraction, %: 43.3
- LV end systolic vol, mL: 64.7
- LV end diastolic vol, mL: 114

### Main clinical findings

- Hypertension: clonidine, lisinopril
- Poor cardiac output; milrinone
- Clinically well
- Respiratory: dexamethasone, intubated
- Clinically well

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**Notes:**
- Conversion to SI units follows in parentheses for each laboratory measurement: total WBC, neutrophils, lymphocytes, and platelet count to cells x 10^9/L (0.001); hemoglobin to millimoles per liter (0.6206); D-dimer to milligrams per liter (1.0); fibrinogen to grams per liter (0.01); ferritin, procalcitonin, and troponin-I to micrograms per liter (1.0); LDH, AST, and ALT to microkatals per liter (0.01667); creatinine to micromoles per liter (88.4); urea nitrogen to millimoles per liter (0.3571); and BNP to nanograms per liter (1.0).
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changes and significant respiratory distress (secondary to poor cardiac function and fluid overload), which necessitated intubation. Despite the fact that neither child had a known exposure to someone with COVID-19 nor reported any symptoms suggestive of COVID-19 in the preceding 4 weeks, both had positive immunoglobulin G antibodies against SARS-CoV-2 nucleocapsid and spike proteins with a negative SARS-CoV-2 PCR result. Results of multiplex respiratory viral PCR panels and blood and urine cultures were also negative.

During the initial days of hospitalization at our institution, both children received current standard of care MIS-C treatment, including IVIg, steroids, aspirin, and anti-coagulants. Whereas the patients showed some improvement in overall clinical status, many important clinical and laboratory parameters remained markedly abnormal, especially direct and indirect measures of cardiac dysfunction and/or injury (eg, decreased LV function or need for inotropes, elevated levels of brain natriuretic peptide (BNP) and troponin-I), systemic, cardiac, or endothelial inflammation (eg, elevated levels of C-reactive protein, procalcitonin, ferritin, and total white blood cell count), and endothelial dysfunction (eg, hypotension or need for vasopressors, elevated levels of

![Graphs showing changes in key parameters with remestemcel-L treatment](image-url)

**FIGURE 3**
Changes in key parameters depicted by remestemcel-L treatment day. A–C. Changes in LV ejection fraction (EF) (A), BNP (B), and D-dimer (C) based on remestemcel-L treatment day. Both children showed rapid normalization in LV EF and BNP as well as improvements in D-dimer that were temporally associated with the cell therapy. To convert BNP and D-dimer to nanograms per liter and milligrams per liter, respectively, multiply by 1.0. *First remestemcel-L infusion. † Second remestemcel-L infusion.
D-dimer and fibrinogen). Thus, they were considered for remestemcel-L treatment under the expanded access program and met inclusion and exclusion criteria.

Legal guardians provided written informed consent for study participation. Both children received two intravenous infusions of remestemcel-L separated by 48 hours (patient 1: MUSC hospital days 5 and 7; patient 2: MUSC hospital days 3 and 5). Each infusion contained 2 million cells per kg of body weight administered over 60 minutes. Logistic issues related to cell preparation and administration necessitated patient 1’s second dose be given 24 hours earlier than outlined in the study, representing a minor protocol deviation approved by the sponsor. For consistency between cases, the same time interval was used for patient 2. Neither child experienced any adverse effects associated with remestemcel-L administration.

Both children showed rapid normalization of their LV ejection fraction and B-type natriuretic protein as well as improvement in D-dimer that were temporally associated with remestemcel-L treatment (Fig 3). In addition, serial echocardiographic imaging revealed reduction in the severity of paravalvular regurgitation as well as increases in LV end systolic vol. The latter observation is consistent with improvement in LV contractile state that was temporally associated with the cell therapy administration. Of note, neither child exhibited coronary artery dilation nor a hemodynamically significant pericardial effusion at any point.

Both children developed rebound hypertension after resolution of their hypotension, potentially reflecting the interaction between restored cardiac output and continued systemic endothelial dysfunction. Patient 2 required prolonged pharmacologic treatment of her hypertension. Patient 1 had an accompanying bradycardia, which resolved shortly after his first dose of remestemcel-L. He also developed symptomatic anemia on hospital days 7 to 8, which was treated with packed red blood cells. This complication was determined to be secondary to a low baseline hemoglobin related to his underlying condition combined with frequent blood draws required for laboratory monitoring and unrelated to remestemcel-L.

The children continued to show clinical and laboratory improvements and were well-appearing by day of discharge (MUSC hospital days 9 and 10, respectively). Both children continue to be managed as outpatients and are doing well (to date, both are ≥90 days out from first remestemcel-L dose). Importantly, both children tolerated remestemcel-L well with no adverse effects, consistent with remestemcel-L’s previously reported favorable safety profile in children.24

**DISCUSSION**

Although both children were showing some level of clinical improvement when they received the experimental product, the data suggest that remestemcel-L contributed to further improvements in myocardial and endothelial function and promoted additional reductions in systemic and cardiac inflammation. Within 1 day of his first remestemcel-L treatment, patient 1’s D-dimer levels decreased from levels that were above the measurable range to values that were rapidly approaching normal. The most likely mechanisms of action that facilitated these improvements include multitargeted, beneficial anti-inflammatory effects that promote endothelial function and protect cardiomyocytes from apoptosis and fibrosis. The mesenchymal lineage cells in remestemcel-L are part of the body’s armamentarium for repairing damaged tissue and restoring normal function. When administered intravenously as described here, MSCs traffic to various organs and lymphoid tissue involved in the inflammatory process and downregulate production of pro-inflammatory cytokines, promote production of anti-inflammatory cytokines, and enable recruitment of naturally occurring anti-inflammatory cells to affected tissues. MSCs produce sustained anti-inflammatory effects, including conversion of Th17 cells to anti-inflammatory FOXP3 T-regulatory cells and conversion of inflammatory M1 macrophages to anti-inflammatory M2 macrophages.19,21,22 In addition, they have revealed beneficial effects on endothelial dysfunction in preclinical and clinical studies.10,20 On the basis of these properties and our successful treatment in two children, remestemcel-L may be a promising and effective treatment of MIS-C, especially in children with significant cardiovascular involvement.

Our two cases highlight several critical themes regarding MIS-C. First, it can develop quickly as a life-threatening illness with cardiovascular collapse in previously healthy children. Second, as revealed in our patients who had multiple encounters with various health care providers before their admission to MUSC, the diagnosis of MIS-C is challenging and can be overlooked. This may be particularly true when traditional KD features like rash, conjunctivitis, and mucous membrane involvement are absent, as in our two cases. Nevertheless, it is important to consider MIS-C in the differential diagnosis for any child who presents with an acute viral-like syndrome, especially in a child with a fever and elevated inflammatory markers. Prompt recognition and initiation of MIS-C treatment is crucial. Third, long-term effects of MIS-C are largely
unknown; however, permanent sequelae are likely in some children. In our cases, patient 2 still required anti-hypertensives and patient 1’s LV ejection fraction declined to the low normal range weeks after hospital discharge. Although speculative, our two patients may have fared far worse without remestemcel-L treatment.

Interestingly, the remestemcel-L doses were given 48 hours apart in these two cases, representing a slightly shorter time interval than what has been previously used for steroid-resistant graft-versus-host disease. Although this alternative dosing schedule was unplanned, the concept of a “rapid sequence” of doses may actually be beneficial in MIS-C given its rapid disease progression and hyperacute inflammatory state. The shorter interval between doses appeared safe and efficacious in our two children and should be considered in the design of future trials for MIS-C and other acute inflammatory conditions.

MIS-C has emerged as another consequence of the devastating COVID-19 pandemic. There are currently no standardized or approved treatments for MIS-C. And, yet, with the continuing surge of COVID-19 cases worldwide, cases of MIS-C will likewise climb. Remestemcel-L exhibits beneficial effects relative to the cardiac and vascular pathophysiology associated with MIS-C and an excellent safety profile in children. This therapy holds promise as a novel treatment of MIS-C.

ACKNOWLEDGMENTS

We thank Dr Michelle Hudspeth and our investigational drug services for sharing their experience and expertise in using remestemcel-L in children with graft-versus-host disease. We thank the families of these children for their willingness to participate in the study and to share their stories about MIS-C and remestemcel-L.

ABBREVIATIONS

- BNP: brain natriuretic peptide
- COVID-19: coronavirus disease 2019
- IVIg: intravenous immunoglobulin
- KD: Kawasaki disease
- LV: left ventricular
- MIS-C: multisystem inflammatory syndrome in children
- MSC: mesenchymal stromal cell
- MUSC: Medical University of South Carolina
- PCR: polymerase chain reaction
- SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

POTENTIAL CONFLICT OF INTEREST: Dr Borow is a consultant to Mesoblast, Inc; Ms Burke is an employee of Mesoblast, Inc; and Drs Eckard, Mack, and Atz have indicated they have no potential conflicts of interest to disclose.

REFERENCES


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