

Targeting Transforming Growth Factor-beta for Treatment of COVID-19-associated Kawasaki Disease in Children

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Some children with COVID-19 have developed a “multi-system inflammatory syndrome” with potentially life-threatening complications requiring hospitalization. In many of these pediatric COVID-19 patients, the presenting signs and symptoms (e.g., bilateral bulbar conjunctival injection, oral mucous membrane changes, including injected pharynx, or strawberry tongue, erythema of palms or soles, edema of hands or feet, polymorphous rash, and cervical lymphadenopathy) were consistent with Kawasaki disease (KD).^[1,2]

KD is a systemic vasculitis often associated with cardiac complications, including myocarditis and coronary artery (CA) abnormalities, such as dilatation, aneurysm, and/or stenosis, left ventricular dysfunction, pericardial effusion, and mitral valve insufficiency.^[3-5] Small CA aneurysms do not affect the survival outcome of pediatric KD patients; large aneurysms with Z-scores ≥ 10 or an internal diameter > 8 mm, on the other hand, have a high risk of obstruction, require systemic anticoagulation, and can cause sudden death due to myocardial infarction (MI) or arrhythmias.^[6,7]

Acute MI is the main cause of death in KD.^[8-11] Vascular changes also may occur in peripheral arteries and cause ischemia and gangrene due to peripheral arterial blood flow obstruction.^[4] Immediate treatment with intravenous immunoglobulin (IVIG) (2 g/kg) in combination with aspirin (30–50 mg/kg/day) can prevent CA aneurysms.^[10,11] Close monitoring and diligent management of cardiovascular complications are critical for risk mitigation. Although most KD patients present with thrombocytosis, thrombocytopenia

can also occur and may be due to KD shock syndrome^[12,13] or macrophage activation syndrome (also known as secondary hemophagocytic lymphohistiocytosis),^[14-16] associated with hepatosplenomegaly, cytopenias, hypofibrinogenemia (< 1.5 g/L), and hyperferritinemia, two potentially fatal complications that can lead to multi-organ failure.

Noval Rivas *et al.* reported elevated circulating secretory immunoglobulin A (sIgA) in KD patients, as well as elevated sIgA and IgA deposition in vascular tissues in a mouse model of KD vasculitis.^[17] Transforming growth factor-beta (TGF- β) signaling in B-cells plays a pivotal role in the induction of isotype switching to IgA production.^[18-21] Dedobbeleer *et al.* showed that stimulated human B lymphocytes produce active TGF- β from surface GARP/latent TGF- β complexes with isotype switching to IgA production.^[22] A disintegrin and metalloprotease 17 (ADAM17) differentially regulates the TGF- β signaling pathway and has been shown to affect the vascular pathology in KD as well as KD susceptibility through its TGF-Q regulatory effects. Three ADAM17 single nucleotide polymorphisms showed an association with KD risk and KD-related secondary CA lesions.^[23] Recent studies by Shimizu *et al.*^[24] and Lee *et al.*^[25] further confirmed that the TGF- β /SMAD3 signaling pathway plays an important role in KD pathogenesis and that genetic variation in three genes in the pathway (*TGFB2*, *TGFBR2*, and *SMAD3*) influence KD susceptibility, CA aneurysm formation, aortic root dilatation, and response to IVIG therapy. Reminiscent of the cytokine profiles of COVID-19 patients with severe disease, acute KD is characterized by high levels of interleukin (IL)-6, IL-10, tumor necrosis factor-alpha, and TGF- β .^[3] IL-10 and

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IL-17 have both been implicated formation of CA aneurysms complicating KD with a risk of death due to aneurysm rupture and/or atherosclerosis causing MI. IL-10, a pro-inflammatory cytokine elevated in severe COVID-19 cases developing ARDS, has been shown to increase TGF- β production and release, TGF- β receptor II upregulation, and IgA secretion in B cells.^[26]

We recently reported on the clinical impact potential of the first-in-class anti-TGF- β RNA therapeutic trabedersen/OT101 for the treatment of hypoxemic respiratory failure and ARDS in COVID-19 patients.^[27] TGF- β was identified as the exclusive master regulator of the epithelial sodium channel (ENaC).^[27] ENaC internalization by alveolar epithelial cells and its upregulation in ARDS causes an ENaC trafficking defect with a marked reduction in the cell-surface abundance of ENaC on lung epithelial cells, thereby rapidly and substantially impairing alveolar fluid reabsorption in ARDS patients and contributing to the persistence of their pulmonary edema.^[27] Furthermore, lower TGF- β levels correlated with better survival outcomes. The anti-TGF- β RNA therapeutic trabedersen/OT101 exhibited a favorable clinical safety profile in Phase I and Phase II clinical trials in cancer patients^[28,29] and it also exhibited nanomolar *in vitro* potency against SARS-CoV-2.^[27] The correlation of lower BAL fluid TGF- β levels with improved survival of ARDS patients taken together with the potent anti-SARS-CoV-2 activity of trabedersen/OT101 supports the concept of reducing TGF- β levels with trabedersen/OT-101 in COVID-19 patients with ARDS.^[27] Based on the aforementioned role of TGF- β in KD, we hypothesize that trabedersen/OT-101 may emerge as a clinically useful adjunct to the IVIG therapy and best supportive care in pediatric COVID-19 patients who develop KD.

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