Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the editor

Insights into pediatric multi-system inflammatory syndrome and COVID-19

Dear Editor,

Kawasaki Disease (KD) was initially described in 1967 [1]. It is a disease primarily of children between 6 months and 5 years of age and is characterized by high fever, cutaneous rash, “strawberry” tongue, conjunctivitis, lymphadenopathy, and above all, a generalized vasculitis. In a recently published review, KD is thought to be triggered by infectious agents and to involve an inappropriate stimulation of the innate immune system, but the role of the adaptive immune system has not been clarified satisfactorily [2]. Asian children are much more susceptible than Caucasian children, and the frequency is about 10 times higher in Japan than in the US [3]. The generalized vasculitis of KD can lead to coronary artery aneurysms. The treatment of KD has evolved over the years; today the essential therapy is intravenous immunoglobulin (IVIG), which is the immunoglobulin fraction of human serum collected from between 1000 and 15,000 individuals. Over 80% of children undergoing this treatment (sometimes supplemented by aspirin) recover without permanent damage to their blood vessels, but between 15 and 20% of these patients are refractory to IVIG treatment, and have a higher incidence of complications, including coronary artery aneurysms, than do children who are IVIG responsive. A recent study shows that serum interferon gamma (IFNγ) > 7.37 pg/ml and IL-6 concentrations > 70.13 pg/ml before IVIG treatment are prognostic of refractoriness to IVIG treatment. Concentrations of these 2, as well as some other pro-inflammatory cytokines, do diminish after IVIG treatment, even in the refractory patients [4]. The role of the pro-inflammatory cytokines TNFα and IL-1β, as well as the Nod-like receptor protein3 inflammasome in association with this disease has been shown by many other studies [5–7].

During the recent COVID-19 pandemic, a small but significant number of children infected with the SARS-CoV-2 virus have developed a KD-like syndrome. The Royal College of Paediatrics and Child Health (https://www.rcpch.ac.uk/sites/default/files/2020–05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf) suggests the following definition of this new syndrome: (1) A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP, and lymphopenia), and evidence of single or multi-organ dysfunction (shock, cardiac, renal, respiratory gastrointestinal or neurological disorder) and partial or full suggestion of KD, (2) Exclusion of other microbiological origin of symptoms, and (3) May be positive or negative for SARS-CoV-2 PCR testing. It is now named “Pediatric Multi-System Inflammatory Syndrome Potentially Associated with COVID-19.” Treatments have included IVIG, but also anti-coagulation when deemed necessary, as well as anti-IL-6 and anti-IL-1 therapy. Some of the children who tested PCR negative for viral RNA on nasal swabs tested positive for serum antibodies to the SARS-CoV-2 virus. Although most children in hospital care recover, some have coronary artery dilatations, as in standard KD.

Although it remains to be proven, we assume that this COVID-19 associated illness and standard KD are sequelae to infections, multiple unknown ones in the case of the latter, and specifically the SARS-CoV-2 virus in the former. One key finding in standard KD is the role played by prostaglandin E_2 (PGE_2) [8,9]. All KD patients have increased plasma PGE_2 concentrations compared to normal controls. These levels were higher in patients resistant to IVIG treatment than they were in patients who responded to IVIG treatment. Three weeks post-IVIG treatment the responders’ PGE_2 were back to pre-treatment levels whereas the non-responders remains as high as they were just after (< 3 days) treatment [10]. In this same article, it is shown that IVIG stimulates, in a dose dependent manner, PGE_2 in blood monocytes. Both IVIG and PGE_2 inhibit CD40 ligand on CD4+ T cells, which may contribute to the therapeutic anti-inflammatory effect of IVIG in this disease. This is important because CD40 ligand levels on CD4+ T cells are higher in KD patients than in controls with other sources of fever, and these levels diminish three days after completing IVIG therapy [11]. Moreover, CD40 ligand levels on CD4+ T-cells seem to indicate whether coronary artery disease will be seen or not during the course of the disease [12].

We have recently reviewed the effects of both PGE_2 and PGJ_2 (and its derivatives) in severe inflammatory disease and have argued that the pro- and anti- inflammatory effects of these prostaglandins are so complex that, for clinical use, it would be better to use compounds that stimulate the natural progression of PGE_2 synthesis followed by inhibition of its synthesis, and then appearance of the PGJ_2 and its derivatives, in order to mimic the body’s natural sequence of events when severe inflammation arises [13]. KD and the newly described syndrome associated with COVID-19 are logical diseases to consider using this approach.

In an article submitted for publication, we have outlined some possible compounds which may mimic this natural progression, including interferon beta-1a (IFNβ-1a). IFNβ-1a is induced by viral pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) and are programmed to stimulate the natural sequence of events of prostaglandin synthesis in SARS-CoV and MERS-CoV infections [14,15]. Also, early treatment with the triple combination of antiviral therapy using IFNβ-1b, lopinavir–ritonavir, and ribavirin is effective in shortening the duration of virus shedding, decreasing cytokine responses, alleviating symptoms, and reducing infectiousness of patients [16].

We also suggested the use of the low molecular weight fraction of 5% commercial human serum albumin (LMWF5A) as a therapeutic which seems to mimic the natural progression of anti-inflammatory timing in response to inflammatory disease. Human serum albumin has been used safely as intravenous therapy of multiple pathological conditions for over 75 y [17]. LMWF5A, obtained from removing the > 5 kDa fraction which includes albumin, contains at least 3 separate anti-inflammatory compounds [18]. The full panoply of anti-inflammatory results found in a large number of cell types was recently published [13]. What we want to emphasize here is that LMWF5A is unique

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among non-steroidal anti-inflammatory compounds. In vitro, it does not inhibit COX-2 expression but instead inhibits TNFα expression while stimulating both PGE_2 and PGJ_2 synthesis, similar to a natural immune response progression. In addition, it is particularly well suited to potential treat KD patients since it reduces leakage in endothelial cells challenged with a pro-inflammatory stimulus [19]. In addition to the acetylation of alpha-tubulin, the LMWF5A alters the actin cytoskeleton of endothelial cells, thereby increasing endothelial barrier function [20].

A variety of human in vitro immune models indicate that LMWF5A reduces the production of pro-inflammatory cytokines implicated in cytokine storm associated with COVID-19. Furthermore, evidence suggests LMWF5A also promotes the production of mediators required for resolving inflammation and enhances the barrier function of endothelial cultures. A more detailed description of the nebulized form trial protocol and rationale was recently published [13]. Although a nebulized form of LMWF5A has been proposed to treat COVID-19 respiratory disease, it seems more likely that intravenous therapy, either alone or as a supplement to IVIG therapy would be a more reasonable approach for a trial in KD patients and the recently observed SARS-CoV-2 associated disease. It would even be feasible to start such a trial on patients who were non-responders to standard IVIG therapy.

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