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Review of available therapies for the treatment of pediatric COVID-19-associated polyarticular inflammatory syndrome

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Abstract

Recently, there have been an increasing number of reports from around the world describing children and adolescents with multisystemic inflammatory conditions associated with COVID-19. The clinical features of these pediatric cases are both similar to and different from other well-described inflammatory syndromes, including Kawasaki disease. Symptoms appear to develop after infection, rather than in the acute phase of COVID-19. Regarding the clinical spectrum, much remains unknown.

The new disease entity challenges specialists around the world in developing universal management protocols. In the fight for the health and lives of patients, treatment according to standard protocols for Kawasaki disease has been used. However, further

clinical trials are required to prove the effectiveness and safety of these treatments. There are reports of successful therapy using intravenous immunoglobulin preparations and steroid therapy. Biologic, antiviral, antibiotic, antiplatelet and anticoagulant therapies are also used. The described pediatric disease can be associated with hemodynamic failure, so treatment should take place in a hospital setting, under the watchful eye of a multidisciplinary team.

Keywords: MIS-C, PIMS-TS, COVID-19

1. Introduction

The rapid spread of acute respiratory infectious disease caused by SARS-CoV-2 virus infection has led to a global pandemic. We are seeing a widespread disease burden on patients worldwide [1].

Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) is a new disease with a relatively small number of described cases. In the literature, one can also find the name MIS-C (multisystem inflammatory syndrome in children), which refers to the same condition [2]. Many of the symptoms present in PIMS-TS are also characteristic of the previously known Kawasaki disease, so the first cases were not correctly diagnosed. Positive tests for antibodies to SARS-CoV-2, combined with a characteristic set of symptoms, allowed the isolation of this new disease entity, affecting children worldwide [3].

Preliminary definitions have been published by the UK's Royal College of Pediatrics and Child Health (RCPCH), the US Centers for Disease Control and Prevention (CDC) and the WHO [2]. The first case of PIMS-TS was reported on April 7, 2020 in the US. It

was a 6-month-old girl with persistent fever, who was initially diagnosed with Kawasaki disease and SARS-CoV-2 infection (positive RT-PCR test) [1]. It has been noted that a sudden increase in morbidity occurs about 4-5 weeks after the peak of COVID-19 cases, with the vast majority of reports coming from countries particularly affected by the COVID-19 pandemic [3, 4, 5].

An analysis of the cases described in the literature noted that fever is one of the most common symptoms. In addition, gastrointestinal symptoms, rashes, conjunctivitis, among others, were reported. The most frequently described physiological abnormality was cardiovascular dysfunction, less frequently respiratory disorders. Affected organs could also include the neurological and urinary systems. Indicators of inflammation increased in most cases. Echocardiographic studies showed abnormalities in the form of coronary aneurysms and pericardial effusions [3, 6, 7, 8].

The described pediatric disease is often associated with hemodynamic failure, including acute cardiac dysfunction requiring hemodynamic support in 60% to 75% of cases. Evidence on the most effective therapies is still lacking, but British studies consistent with Delphi indicate intravenous immunoglobulin administration as initial therapy [2, 9].

2. Material and method

The purpose of this paper is to present the current state of knowledge on the treatment of pediatric polyarticular inflammatory syndrome associated with COVID-19. Using the PubMed platform, publications outlining the latest options and methods used to treat PIMS-TS and MIS-C were reviewed. The search included the keywords "MIS-C," "PIMS-TS," "COVID-19."

3. Treatment used

3.1 Immunotherapy (IVIG)

The British model of management developed by the Delphi method implies that a multidisciplinary team is essential in the care of children with PIMS-TS. The patient

should be discussed within 24 hours of suspected onset. Therapeutic choices should depend on the phenotype presented (Kawasaki disease-like presentation, defined using criteria published by the American Heart Association, or non-specific) and high-risk features or disease severity. The distinction between phenotypes is based on expert opinion, as the biological mechanisms of PIMS-TS have yet to be elucidated. Initial assessment helps clinicians determine the need for immunoglobulin administration. Intravenous immunotherapy is indicated in all children with a phenotype similar to Kawasaki disease. However, it is not recommended for every child with a nonspecific presentation - in this case, IVIG treatment is indicated when there is evidence of disease management, coronary artery abnormalities are present, criteria for toxic shock syndrome are met, and the duration of fever is prolonged (>5 days). The preferred dose of the preparation is 2 g/kg of calculated ideal body weight. Depending on the clinical picture, it can be administered in a single dose or in a divided dose [2].

Many cases met diagnostic criteria for classic or incomplete Kawasaki disease. Most patients with MIS-C were treated with the standard protocol for Kawasaki disease, which is primarily intravenous immunoglobulin [2,16]. Immunoglobulins are antibodies synthesized by B lymphocytes - plasma cells that can recognize a broad spectrum of specific antigenic determinants. This ability is the basis of the humoral immune response. The IgG subclasses in IVIG products have an appropriate distribution - similar to that found in human plasma. IVIG therapy works by binding its Fc fragment to Fc-gamma receptors on inflammatory cells [10]. There are cases of non-response to the administered product. Resistance to therapy can be seen in patients with anemia, neutrophilia, hypoalbuminemia, elevated levels of interleukin-6 and CRP [11].

Clinical trials have shown that widely used immunoglobulin therapy is well tolerated. However, various side effects have been reported. These include hot flashes, headache, malaise, fever, chills, fatigue and lethargy. Most of these events were mild and transient. Rare side effects we can include renal dysfunction, thromboses, arrhythmias, aseptic meningitis, hemolytic anemia and acute post-transfusion lung injury. For IGIV infusions, systemic adverse effects can be immediate (60% of reactions) - occurring within 6 hours of infusion, delayed (40% of reactions) - manifesting from 6 hours to 1 week after administration, and late (less than 1% of reactions) - arising weeks to months after infusion [12, 13].

3.2 Steroid therapy

Steroid therapy for the treatment of pediatric COVID-19-associated polyarticular inflammatory syndrome is considered as an adjunct or second-choice therapy. Patients presenting features of the Kawasaki disease-like phenotype who can be classified as high-risk (age less than 12 months and the presence of coronary artery lesions) are recommended to receive methyloperdnisolone at a dose of 10-30 mg/kg of ideal body weight along with intravenous immunoglobulin. It should also be considered as another treatment option for any children who feel unwell 24 hours after immunoglobulin infusion, especially if they have a persistent fever. Gastroprotection (e.g. omeprazole) is indicated in children who are taking high doses of steroids [2].

The French Consortium for Childhood Inflammation Covid-19 conducted a study on the relationship of intravenous immunoglobulin (IVIG) used alone and in combination with methylprednisolone. They found that among children with MIS-C, treatment with IVIG along with methylprednisolone was associated with a more favorable course of fever [9, 14]. There are also reports in the literature that IVIG given along with glucocorticosteroids is associated with a lower risk of cardiovascular dysfunction [15].

Methylprednisolone is a systemic synthetic corticosteroid. It exerts a wide range of physiological effects. The clinical use of this agent is mainly due to its anti-inflammatory and immunosuppressive properties. The mechanism of action of this drug is complex. Methylprednisolone diffuses passively across the cell membrane and binds to the intracellular glucocorticoid receptor to form a complex. It then travels to the nucleus, causing enhancement or inhibition of transcription of specific genes. It blocks the promoter sites of pro-inflammatory genes, enhances the expression of anti-inflammatory genes, and reduces cytokine synthesis by blocking the function of transcription factors such as nuclear kappa-B factor. Methylprednisolone can also prevent inflammation by reversing capillary permeability, inhibiting fibroblast and multinucleated leukocyte migration, altering the rate of protein synthesis, and stabilizing lysosomes at the cellular level. It also inhibits cell-dependent immune functions, especially those of lymphocytes, and reduces the synthesis of cyclooxygenase (COX)-2, responsible for the production of prostaglandins in damaged tissue [16, 17, 18].

The UK RECOVERY study, showed that dexamethasone reduces mortality in patients undergoing mechanical ventilation for severe respiratory complications resulting from COVID-19 infection. Its administration to patients with MISC-C may be beneficial in suppressing immune responses and inflammatory disorders [19]. Another study, conducted in a group of 100 patients, 35 of whom received dexamethasone and 65 of whom received methylprednisolone, showed equal efficacy of these drugs in moderate to severe Covid 19 disease. [20].

3.3. Biological therapy

Biologic therapy should be considered as a third-line option in children who do not respond to intravenous immunoglobulin and steroid therapy. The decision to use this modality should be made by a multidisciplinary team. The choice of a particular agent may be dictated by the symptoms presented by the affected child. The preferred biological therapy for children with a phenotype similar to Kawasaki disease is infliximab. The choice of biologic agent in patients who present with nonspecific symptoms should be based on the experience of the clinician. No consensus has been reached on the preferred agent in these cases, and drugs used include tocilizumab, anakinra, and infliximab [2, 21, 22].

Infliximab is a chimeric human-mouse IgG monoclonal antibody made from a recombinant cell line. It was introduced in 1998. The agent captures and neutralizes tumor necrosis factor alpha [TNFα], a key inflammatory cytokine. It also affects the expression of molecules responsible for cell adhesion, chemotacticity and tissue degradation. Treatment is followed by a decrease in IL-6 and C-reactive protein (CRP) levels [23,24]. Tocilizumab is a recombinant humanized monoclonal antibody. It belongs to the IgG immunoglobulin subclass. It was first approved in 2005 in Japan as a treatment for Castleman's disease. The drug works by inhibiting the activity of the pro-inflammatory interleukin-6, by competing with both soluble and membrane-bound forms of the human receptor for this interleukin [25]. Anakinra is an interleukin-1 receptor antagonist, and has been produced by recombinant DNA in the E. coli gene expression system. It is routinely used in patients with autoimmune and inflammatory diseases. The safety of its use, its wide therapeutic margin, and the effect of anakinra on IL-1, justify the use of this

potential therapeutic agent in the treatment of COVID-19-associated multisystem inflammatory syndrome" [26].

3.4 Antiviral and antibiotic therapy

Children with PIMS-TS who are SARS-CoV-2 positive by RT-PCR or antigen tests can be treated with antiviral therapy. The first-line drug of this group is remdesivir [2]. As a nucleotide analog, it exhibits a broad spectrum of activity against viruses from several families. Its action is based on inhibition of viral RNA polymerase. This causes the termination of transcription, which reduces the production of viral genetic material. The drug has been shown to shorten the duration of COVID-19 disease in adults. The role of remdesivir in the treatment of MIS-C is limited because remdesivir actively inhibits viral replication, and most children with MIS-C are not in the acute phase of COVID-19 disease [19]. The safety and efficacy of remdesivir (including in pediatric patients and in combination with anti-inflammatory drugs) are still being evaluated in ongoing clinical trials. The agent is administered intravenously and is available as a solution or lyophilized powder for infusion. In July 2020, it was announced that inhaled remdesivir solution for the potential outpatient treatment of COVID-19 is in the first phase of development. Determination of renal and hepatic function is required before initiating treatment. Remdesivir should not be used in patients with estimated glomerular filtration rate (eGFR) < 30 ml/min or those with alanine aminotransferase (ALAT) ≥ 5 times the upper limit of normal [27].

All children with PIMS-TS should be treated for suspected sepsis until microbiological culture results are available. Intravenous antibiotic therapy should be administered based on clinical presentation and culture results. For children who meet the criteria for toxic shock syndrome, clindamycin is recommended in addition to broad-spectrum antibiotics [2].

3.5 Antiplatelet and anticoagulant therapy

Because of meeting the diagnostic criteria of classic or incomplete Kawasaki disease, most of the reported cases of MIS-C were treated with the standard protocol for the aforementioned acute inflammatory disease of the small and medium vessels - intravenous immunoglobulin along with acetylsalicylic acid (ASA) [20]. It seems that low doses of ASA should be continued for at least 6 weeks in all patients with PIMS-TS. Children who have experienced a thrombotic incident should be treated according to local guidelines for the management of the event. Patients older than 12 years are advised to wear compression stockings [2]. A cross-sectional study of children's hospitals in the US on management protocols for patients with MIS-C showed that acetylsalicylic acid was commonly included, even in mild conditions, while unfractionated heparin or low-molecular-weight heparin was used mainly in severe cases [28].

The laboratory method of synthesizing acetylsalicylic acid was developed in the 19th century. Bayer introduced this preparation under the trade name "Aspirin" - Therefore, colloquially, the term "aspirin" is often used for drugs containing acetylsalicylic acid in their composition. This substance has long been considered a useful analgesic, antipyretic and anti-inflammatory. The anticoagulant effect of aspirin was first described by Lawrence Craven. The basis of the mechanism of action of this drug is the inhibition of the activity of cyclooxygenases (COX-1 and COX-2), enzymes involved in the synthesis of prostaglandins and thromboxane from cell membrane lipids. The anti-aggregation effect is possible due to irreversible inhibition of platelet COX-1 and attenuation of thrombinogenesis (thromboxane synthesis). In platelets, irreversible inhibition of COX-1 is of particular importance, since the synthesis of any new enzyme in these cells is negligible. This feature of platelets leads to a more profound and prolonged inhibition of their function compared to the effect of ASA on cells containing nuclei. It is now accepted that daily low doses of aspirin can prevent myocardial infarction and stroke [29].

4 Conclusions

Childhood multisystemic inflammatory syndrome associated with COVID - 19 is a new disease entity that threatens the lives of children and adolescents. Patients should be treated in the hospital setting. Regardless of the severity of the disease, vigilance for complications is recommended for all patients. Continued research into the cause, course and possible therapies for this condition is essential. To date, the most effective treatment strategy has not been established, and therapeutic choices depend on the symptoms presented and high-risk features. Treatment pathways should be updated as new evidence emerges.

Author's contribution

Conceptualization, Michał Leśniewski; methodology, Michał Leśniewski; software, Michał Leśniewski; check, Michał Leśniewski; formal analysis, Michał Leśniewski; investigation, Michał Leśniewski; data curation, Michał Leśniewski; writing – rough preparation, Michał Leśniewski; writing – review and editing, Michał Leśniewski; supervision, Michał Leśniewski; project administration, Michał Leśniewski; receiving funding, Michał Leśniewski.

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