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REVIEW

Drugs for paediatric hyperinflammatory syndromes

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Abstract

Background: Many syndromes are associated with exaggerated inflammation. Children with hyperinflammatory syndromes often present with vague and non-specific symptoms that pose diagnostic and management challenges. The recent literature seems biased towards referring these syndromes only to the multisystem inflammatory syndrome in children (MIS-C) that is associated with COVID-19. The purpose of this paper is to provide an updated narrative review on the pathophysiology, manifestations and management approaches for common hyperinflammatory syndromes.

Methods: An extensive PubMed search of all publications in the English literature was performed with Clinical Queries for various hyperinflammatory syndromes and conditions using the undermentioned Medical Subject Headings: "hyperinflammation", "hyperinflammatory syndromes", "sepsis syndrome", "severe inflammatory response syndrome" and "acute respiratory distress syndrome". Categories were limited to reviews and clinical trials for the age range from birth to 18 years.

Results: The criteria, presentation and management of these hyperinflammatory syndromes are described. Hyperinflammatory syndromes refer to a basket of inflammatory syndromes often associated with multisystem involvement and aberrant cytokine release and should be differentiated from autoinflammatory, autoimmune and hyperimmune syndromes. The major subtypes of hyperinflammatory syndromes, including macrophage activation syndrome, haemophagocytic lymphohistiocytosis, cytokine release syndrome and cytokine storm syndrome, are described. MIS-C associated with SARS-CoV-2 represents the latest addition. It must be understood that the syndrome is not exclusive to COVID-19 but could be caused by various viral infections. Early recognition, prompt and proactive treatment can reduce potential complications and improve outcomes and survival rates in paediatric patients. Anti-inflammatory medications for the management of these syndromes are described.

Conclusion: The incidence of these hyperinflammatory conditions is generally low in comparison to other disease conditions. Except for paediatric inflammatory multisystem syndrome/MIS-C, the mortality is high and the hospital stay is prolonged in affected patients. Acute and critical care physicians must be aware of these conditions and their initial management. Corticosteroids are often used in the initial phrase but various disease-specific drugs and biologics are needed in subsequent management and expert management of these often-difficult conditions is crucial.

Keywords: COVID-19, cytokine release syndrome, cytokine storm syndrome, haemophagocytic lymphohistiocytosis, hyperinflammatory syndromes, macrophage activation syndrome, multisystem inflammatory syndrome in children.

Citation

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Introduction

Children with hyperinflammatory syndromes often present with vague and non-specific symptoms that pose diagnostic and management challenges.[1–3] These syndromes are unfamiliar to most acute care physicians. Prompt and appropriate management is critical as it determines the clinical course and eventual clinical outcome. Clinically, they often present with pyrexia or fever of unknown origin, vague non-specific symptoms, and evidence of exaggerated inflammation, which can occur in multiple organs.[4] Malignancy and serious infection need to be considered and promptly managed. A multidisciplinary team approach is mandatory in the management of these patients.

Methods

An extensive PubMed search in the English literature of human studies was performed with Clinical Queries for various hyperinflammatory syndromes using the following medical subject headings: "hyperinflammation", "hyperinflammatory syndromes", "sepsis syndrome", "severe inflammatory response syndrome" and "acute respiratory distress syndrome". Categories were limited to reviews and clinical trials for the age range from birth to 18 years.

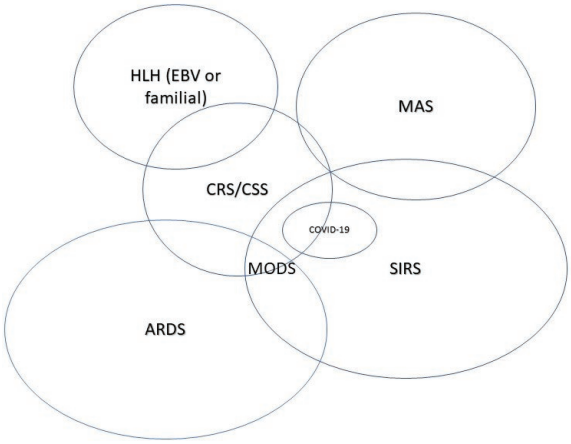
Hyperinflammatory *versus* autoimmune and autoinflammatory diseases

Inflammation is a complex biological protective reaction of body tissues to noxious stimuli, including irritants, pathogens, tissue hypoxia and oxidative stress, and involving immune cells, blood vessels as well as molecular mediators.[5] T cell-dependent response is classified as type 1 and 2 based on the helper T cells (T_H1 and T_H2) and cytokines involved.[6,7] The functions of T cell-mediated inflammatory response are to eliminate the cause of cell injury, necrotic cells, tissues and debris damaged from the inciting insult. Tissue repair is then initiated. Inflammatory responses can be autoimmune, autoinflammatory or hyperinflammatory. These responses are generally distinct entities, though they may overlap with each other.

An autoimmune disease is a disorder of multifactorial origin arising from dysregulated immune response against a functioning organ or tissue.[8] Type III hypersensitivity mechanisms are often involved in its pathophysiology such as the prototypic disease systemic lupus erythematosus (SLE). Some autoimmune diseases are familial and others may be triggered by environmental factors or infections.[8] Some relatively common autoimmune diseases include SLE, Graves' disease, type 1 diabetes mellitus, coeliac disease, inflammatory bowel disease, psoriasis, multiple sclerosis and rheumatoid arthritis.[8,9] The initial diagnosis can be challenging and difficult as they may masquerade as many inflammatory and infectious diseases.[8] Non-steroidal anti-inflammatory drugs and immunosuppressant medications are often used, depending on the type and severity of the condition.[8] Intravenous immunoglobulin may be needed.[10] Treatment is for symptomatic support and to suppress immune dysregulation, though typically not curative.[8]

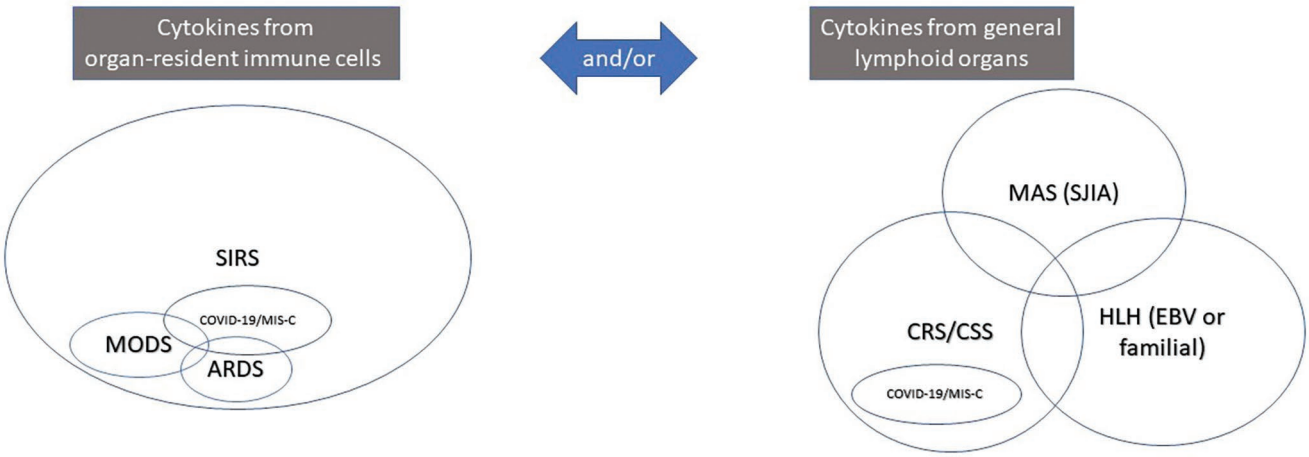
Autoinflammatory diseases involve errors or mistakes in the innate immune system.[11] Unlike SLE and various autoimmune disorders that involve aberrations of the adaptive immune system, autoantibodies or antigen-specific T or B cells are not produced in patients with autoinflammatory diseases. Autoinflammatory diseases are diverse and characterized by recurrent episodes of organ-specific and systemic inflammation that cause febrile episodes of skin rashes, arthralgia and abdominal pain. Recurrent inflammation may lead to amyloidosis.[12] Most autoinflammatory diseases present during childhood and have a genetic association.[13] Physicians must consider autoinflammatory diseases in paediatric patients with recurrent, unexplained febrile episodes when malignant and infectious causes have been excluded. Familial Mediterranean fever, periodic fever syndrome, hyper-IgD syndrome, tumour necrosis factor receptor-associated periodic syndrome, cryopyrin-associated periodic syndromes, deficiency of IL-36 receptor antagonist, deficiency of the IL-1 receptor antagonist, chronic atypical neutrophilic dermatosis with lipodystrophy and increased temperature syndrome, and Majeed syndrome are monogenic autoinflammatory diseases with recurrent fevers. The most common genetic autoinflammatory disease is familial Mediterranean fever, which is characterized by recurrent attacks of fever that last less than 72 hours and serosal inflammation as manifested by abdominal and chest pain. Familial Mediterranean fever is due to mutations in the *MEFV* gene, which codes for the protein pyrin normally present inside inflammasomes. Inappropriate activation of the inflammasome is caused by the mutated pyrin protein that leads to inappropriate release of the pro-inflammatory cytokine IL-1β. Inflammasomes are receptors and sensors of the innate immune system implicated in inflammatory disorders that regulate caspase 1 activation and induce inflammation to microbes and host proteins.[14] Many autoinflammatory diseases are pathphysiologically mediated by IL-1β.[15] Therefore, IL-1β is a therapeutic target revolutionized by the treatment with anakinra, rilonacept and canakinumab.

Figure 1. Classification of the inflammatory conditions.



ARDS, acute respiratory distress syndrome; CRS, cytokine release syndrome; CSS, cytokine storm syndrome; HLH, haemophagocytic lymphohistiocytosis; MAS, macrophage activation syndrome; MODS, multiorgan dysfunction syndrome; SIRS, systemic inflammatory syndrome.

Figure 2. Two models of classification of the inflammatory conditions based on cytokines.



ARDS, acute respiratory distress syndrome; CRS, cytokine release syndrome; CSS, cytokine storm syndrome; HLH, haemophagocytic lymphohistiocytosis; MAS, macrophage activation syndrome; MIS-C, multisystem inflammatory syndrome in children; MODS, multiorgan dysfunction syndrome; SJIA, systemic juvenile idiopathic arthritis; SIRS, systemic inflammatory syndrome.

Hyperinflammatory syndromes refer to a basket of inflammatory syndromes often associated with multisystem involvement and aberrant cytokine release. The concept of hyperinflammation is not novel and stems from the observation in the 2003 SARS epidemic.[3] Various models of classifications based on the pathophysiology of cytokine generations have been proposed (Figures 1 and 2). Multisystem inflammatory syndrome in children (MIS-C) has been coined as a syndrome since the coronavirus disease 2019 pandemic (COVID-19). MIS-C was first reported in 2020 as a hyperinflammatory syndrome with several features resembling Kawasaki disease.[2] Most cases occur several weeks following SARS-CoV-2 infection in persons younger than 21 years of age with severe illness. MIS-C involves older often previously healthy non-Asian children and young adults, distinguishing it from Kawasaki disease.[16,17] Of note, post-COVID paediatric inflammatory multisystem syndrome – temporally associated with SARS-CoV-2 (PIMS-TS) or MIS-C should be differentiated from the acute (severe) coronavirus disease of COVID-19, Middle East respiratory syndrome (MERS) and SARS. Both have distinctly different features, presentations, epidemiology and (incompletely understood) pathophysiology.

The concept of hyperinflammation and autoinflammation syndromes are complicated and beyond the scope of this narrative review article on medical therapeutics. Only syndromes of hyperinflammation but not autoimmune and autoinflammatory diseases are discussed in detail herein. Specifically, systemic inflammatory response syndrome (SIRS), haemophagocytic lymphohistiocytosis (HLH) and macrophage-activation syndrome (MAS), cytokine release syndrome/cytokine storm syndrome (CRS/CSS), and COVID-19-related syndromes will be discussed.

Syndromes associated with hyperinflammation

SIRS

SIRS is a generalized inflammatory state in response to a noxious infectious or non-infectious insult.[18] SIRS is a clinical entity characterized by ≥2 of 4 criteria (one criterion must be abnormal temperature or leukocyte count): core temperature higher than 38°C or lower than 36°C; respiratory rate >20 breaths/minute or $PaCO_2$ less than 32 mmHg; heart rate greater than 90 beats/minute; and white cell count higher than 12,000/mm^3, lower than 4000/mm^3, or higher than 10% bands or immature forms.[19] SIRS is considered a clinical manifestation of a severe cytokine storm, in which the duration of cytokine activation is actually longer than clinical signs of SIRS criteria.[20] SIRS is related to sepsis in that patients may have a suspected or proven infection.[21,22]

CRS and CSS

CRS refers to a type of SIRS that is triggered by an infection or certain drugs. Severe or acute CRS is termed CSS. Acute respiratory distress syndrome (ARDS) can be part of these multiorgan dysfunction syndromes (MODS) as a result of endothelial and epithelial cell injury of the pulmonary tissue increasing alveolar capillary permeability, thereby resulting in pulmonary oedema.[23,24] Symptoms of CRS could be delayed after treatment with some drugs. Immediate-onset (fulminant) CRS is likely a CSS. CSS is due to deranged innate immune system and is a severe form of CRS or a component of MAS, characterized by raised serum levels of ferritin, aspartate aminotransferase, D-dimer, C-reactive protein (CRP), procalcitonin, lactate dehydrogenase, neutrophils and

creatinine.[25–27] Serum ferritin, IL-6 and CRP are particularly raised in CSS associated with COVID-19.[28]

HLH and MAS

HLH is a CSS that is a life-threatening haematologic disease of severe hyperinflammation due to uncontrolled proliferation of macrophages, activated lymphocytes and production of inflammatory cytokines.[29–33] The case definition requires a molecular diagnosis of HLH-associated gene mutations (i.e. *PRF1*, *STX11* or *UNC13D*) or five of eight of the following criteria: (i) fever higher than 38°C, (ii) splenomegaly, (iii) diminished blood cell counts involving at least two of three peripheral blood lineages: anaemia with haemoglobin less than 9 g/dL or haemoglobin less than 10 g/dL in infants less than 4 weeks old, thrombocytopenia with platelets less than 100×10^9/L, or neutropenia with neutrophils less than 1×10^9/L, (iv) high blood triglyceride levels (fasting levels ≥265 mg/dL) and/or ferritin ≥500 ng/mL, (v) decreased blood fibrinogen (≤150 mg/dL), (vi) haemophagocytosis (evident in the bone marrow, spleen or lymph nodes), (vii) absent or low natural killer cell activity, and (viii) soluble IL-2 receptor (CD25) levels greater than 2400 U/mL.

HLH is an uncontrolled severe hyperinflammatory response that occurs in many conditions.[31] Genetic types of HLHs are caused by defects in function, processing and transport of cytotoxic granules in cytotoxic T lymphocytes and natural killer cells.[34] Acquired types of HLH are seen in acquired immune deficiency, autoimmune diseases and autoinflammatory diseases, infections, and malignancies. Functional tests may differentiate between acquired and genetic types of HLH. Treatment aims to suppress hypercytokinaemia and eliminate infected and activated cells and includes immunosuppressive and immunomodulatory agents, cytostatics, and cytokine and T cell cytokine antibodies.[34] Cure can only be achieved with haematopoietic stem cell transplantation in genetic forms of HLH. Conditioning regimens with reduced intensity have substantively improved patient survival.[34]

MAS is a potentially life-threatening complication of a few chronic childhood rheumatic diseases like Kawasaki disease, SLE, systemic-onset juvenile idiopathic arthritis and adult-onset Still's disease. Pathophysiologically, MAS is similar to reactive or secondary HLH and is associated with several genetic defects that profoundly depress the cytolytic pathway, distinguishing the condition from other rheumatic diseases.[35] Haemophagocytic macrophages are expanded and express a scavenger receptor (CD163) that initiates pathways important for adaptation to oxidative stress. In contrast to MAS, MIS-C, CRS, CSS and SIRS are unlikely associated with cytopenia.[30,35,36] MAS is characterized by fever, ferritin higher than 684 ng/mL plus any two of the following: haemoglobin <90 g/L and <100 g/L in infants less than 4 weeks, neutrophils less than 1.0×10^9/L, platelets less than 100×10^9/L, fasting triglycerides ≥3.0 mmol/L (i.e. ≥265 mg/dL) and fibrinogen ≤1.5 g/L.[30,35,36] Other markers of lymphocyte activation (soluble IL-2 receptor) and macrophage activation (soluble CD163) are associated. In addition, depressed natural killer (NK) cell function (by NK cell function analysis) or depressed NK cell population (by flow cytometry) may be shown.[37] Other features include reduced erythrocyte sedimentation rate (which may be increased if the underlying driver is systemic-onset juvenile idiopathic arthritis/SLE), hyperferritinaemia, hepatopathy, coagulopathy, thrombocytopenia, hypertriglyceridaemia and bone marrow haemophagocytosis.

COVID-19 syndromes

Many syndromes have been coined for outbreaks of coronavirus diseases, namely SARS in 2003, MERS in 2011, and COVID-19 in 2019, with the subsequent related syndromes of MIS-C, paediatric multisystem inflammatory syndrome (PMIS), PIMS temporally associated with SARS-CoV-2 (PIMS-TS), COVID toe syndrome, COVID ageusia and COVID anosmia.[3,38] MIS-C syndrome was first proposed by the Royal College of Paediatrics and Child Health in early 2020. Interestingly, in the initial case definition, SARS-CoV-2 PCR may be positive or negative and not mandatory for diagnosis. The subsequent World Health Organization (WHO) and US Centers for Disease Control and Prevention (CDC) definitions both require presence of evidence of SARS-CoV-2 infection. The other acronyms include PMIS and PIMS-TS.[39] MIS-C, PMIS and PIMS-TS are all coined abbreviations or acronyms to describe a multisystemic disease involving fever, exaggerated inflammation and multiorgan dysfunction correlated with SARS-CoV-2 exposure/infection. This syndrome has been considered to resemble Kawasaki disease, SIRS and MAS.[39–42] The case definition and association between MIS-C and COVID-19 remain controversial and confusing.[23,43,44]

Several grading terms have been used to describe the same clinical presentation, including SIRS, severe sepsis, septic shock, recalcitrant septic shock, toxic shock syndrome and even MODS.[24] Generally, there should be persistent fever >38.5°C and inflammation with one or more organs in dysfunction with additional clinical features such as increased serum ferritin, IL-6 and CRP in the case of CSS.[28,39]

Severe COVID-19 is probably a cytokine storm due to a hyperinflammatory reaction. The apparent link between this paediatric hyperinflammatory syndrome and COVID-19 could be attributed to the similarities in presentations between COVID-19 and many of the sepsis syndromes, including SIRS, toxic shock syndrome, Kawasaki disease shock syndrome and MODS. Considerable evidence has also suggested that COVID-19 infection is a hypercoagulable state as reflected in the extremely elevated levels of a marker of clot turnover (D-dimer) in many patients over the first few weeks of disease.[45,46] Furthermore, the increase in NT-proBNP in those patients appears to confirm the pivotal role of the NO–cGMP axis, which would lead to thrombotic complications.[47,48] Many common respiratory viruses, including enterovirus adenovirus, rhinovirus, RSV and coronaviruses, have been reported to be associated with Kawasaki disease;[3,49,50] SARS-CoV-2 is just

one of the respiratory viruses associated with the paediatric hyperinflammatory syndromes PMIS, MIS-C, PIMS-TS, Kawasaki disease shock syndrome, CRS or CSS.[50–52] Finally, obesity and metabolic syndromes are also known to be associated with inflammation.[53]

As aforementioned, the entity of post-COVID PIMS-TS/MIS-C should be differentiated from the acute (severe) coronavirus disease due to SARS-CoV-2, MERS and SARS.

In summary, HLH is a form of CSS and a life-threatening haematologic disorder of hyperinflammation as a result of uncontrolled proliferation of activated lymphocytes, macrophages and production of inflammatory cytokines.[54] Separately, MAS is a severe, life-threatening complication of chronic childhood rheumatic diseases that may be associated with SLE, Kawasaki disease or MAS,[42] which is pathophysiologically very similar to reactive or secondary HLH. Finally, CRS is a form of SIRS that can be triggered by a myriad of factors such as some infections and drugs. Severe and acute CRS is termed CSS. ARDS can be part of all these MODS.[23,24,55] Finally, PIMS-TS/MIS-C and the acute (severe) coronavirus diseases of COVID-19, MERS and SARS are probably separate entities that need further delineation for research and therapeutic purposes.

Frontline and acute care physicians must be familiar with these seemingly different syndromes of hyperinflammation among sick children in order to provide prompt and timely treatment.[56] The definitions invariably include evidence of inflammation, such as fever, inflammatory markers and organ system dysfunction, with or without evidence of concurrent or recent infection. Treatment is mainly organ supportive but also includes the use of immunomodulatory and anti-inflammatory drugs. Children with these syndromes often present with vague and non-specific symptomatology that poses diagnostic and therapeutic challenges to acute care physicians.[23] The initial hours of management are critical as they determine the clinical course and eventual clinical outcome. During the COVID-19 pandemic, we encountered several cases of children negative for SARS-CoV-2 with ARDS, HLH-like disease and CSS and faced two confusing but inter-related issues, namely the conflation of various hyperinflammatory syndromes and whether they could be caused by pathogens other than coronavirus infection.[38,57]

Management of hyperinflammatory diseases

General management

Hyperinflammatory diseases have a number of issues in common, including pyrexia of unknow origin, vague presentation and involvement of various organs, and often delayed presentation (presumably because parents often seek symptomatic treatment with general practitioner or complementary and alternative therapies first). As such, making a definitive diagnosis and timely management in the initial phase can be challenging. Physicians must rely on their clinical acumen to recognize the possibility of an underlying hyperinflammatory syndrome in these situations. To make matter worse, the definitions of many of the hyperinflammatory syndromes and acronyms are poorly defined and overlapping. There are several concepts of classification, based on the origin of cytokines, loss of function *versus* gain of function, or innate *versus* adaptive dysfunction.[58] Figures 1 and 2 represent two possible classifications that we believe would help the understanding of the various hyperinflammatory conditions.

The key to managing suspected hyperinflammatory conditions before the availability of a definitive diagnosis is to stabilize the major organ systems and to treat potential life-threatening infection. The most likely diagnosis may be inferred clinically according to latest definition of these syndromes and initial routine laboratory investigations. Treatment for SIRS is directed towards the underlying inciting cause.[22] There is some evidence that glutamine, selenium, eicosapentaenoic acid and vitamin E are effective in improving clinical symptoms in trials.[59–62]

For acute care physicians, the general treatment strategy for these syndromes, with or without cytokine storm, is supportive treatment to maintain vital organ function and removal of triggers for aberrant immune system activation. A multidisciplinary approach often involves the rheumatologist, oncologist, immunologist and intensivist to provide non-specific immunosuppression or targeted immunomodulation to limit the collateral damage of the activated hyperinflammatory immune system.[25]

Drugs

Several drugs are efficacious across multiple disorders with CSS.[25] The use of immunosuppressive drugs, such as corticosteroids, and avoidance of drugs that can activate the immune system are important in CRS and CSS.[63] Tocilizumab is an anti-IL-6 monoclonal antibody that has been approved for steroid-refractory CRS.[63,64] Lenzilumab is an anti-GM-CSF monoclonal antibody efficacious at managing cytokine release by reducing myeloid activation and decreasing IL-1, IL-6, IP-10, MIP1 and MCP1 production.[65] Most commonly used treatments for HLH and MAS include high-dose glucocorticoids, cyclosporine or etoposide as a bridge to transplant.[29] Rituximab is effective in Epstein–Barr virus (EBV)-related HLH, and intravenous immunoglobulin (IVIG) may be efficacious in secondary forms of HLH and MAS.[66–68] Anakinra may also be effective in MAS.[54]

A brief overview of some of the medications used in hyperinflammatory syndromes is provided below.

Corticosteroids

Many forms of corticosteroids are used in most inflammatory conditions, including COVID-19, at least in the initial phase of management.[69,70] In one case, dexamethasone was used in a newborn with severe COVID-19 complicated by cerebral venous thrombosis, in combination with anti-SARS-CoV-2 hyperimmune plasma on day 3 and day 4, dexamethasone

0.15 mg/kg/day and remdesivir (2.5 mg/kg on day 5 and 1.25 mg/kg for 9 more days).[71] The neonate survived. Pulsed methylprednisolone is an alternative.[72] In view of the significant side effects of corticosteroids, steroid-sparing agents are usually added on following the initial management of these inflammatory conditions to spare the use of steroids and minimize their side effects.

IVIG

IVIG has been widely used in many conditions associated with inflammation. It is the standard treatment for Kawasaki disease. High-dose IVIG is associated with marked improvement and fever resolution within 24 hours. The unusual dosage is 1 mg/kg daily for 2 days, or 0.5 mg/kg/day for 5 days.[49,72,73] If the fever does not respond to the above dosage schedule, an additional dose may be considered.[73] When administered in the first 10 days of the disease, IVIG reduces the risk of coronary artery damage in patients without serious side effects.[73,74] IVIG is most efficacious when administered within the first 7 days of fever onset for prevention of coronary artery aneurysm. In addition to IVIG for the treatment of Kawasaki disease, a high dose of oral aspirin (acetylsalicylic acid 80–100 mg/kg/day, divided into four doses) is also used for its anti-inflammatory effect and should be continued till the 14th day of illness, or at least 48–72 hours after the cessation of fever.[49]

Cyclosporine

Cyclosporine is no longer used in paediatric or adult juvenile idiopathic arthritis/rheumatoid arthritis (JIA/RA) now with advent of anti-TNF and other biologics. It is only used in context of severe HLH with significant organ burden (e.g. liver/spleen), and no definite reversible infectious trigger.[72] Initial dose is usually 1.25 mg/kg orally given twice a day, with onset of action occurring between 4 and 8 weeks. Dosage is increased by 0.5–0.75 mg/kg/day after 8 weeks and again after 12 weeks if benefit is not observed despite good tolerability at the initial dose (e.g. serum creatinine <30% above baseline). The maximal dose is 4 mg/kg/day orally divided into two doses. Monitoring of the serum drug level is essential. The therapy should be discontinued if no benefit is seen by 16 weeks.

Etoposide

Moderately dosed etoposide (i.e. 50–100 mg/m^2 once weekly) is useful in severe and/or refractory forms of MAS-HLH when conventional MAS-HLH treatment is insufficient.[75] Etoposide is also efficacious when used with cyclosporine, dexamethasone and methotrexate for SLE complicated with MAS mimicking MIS-C.[42]

Tocilizumab

Tocilizumab is an FDA-approved anti-IL-6 monoclonal antibody for steroid-refractory CRS.[63,64] Tocilizumab has been used in patients with SARS-CoV-2 and CCS.[76,77] The suggested dosage of tocilizumab is two 8 mg/kg doses with a maximal dose of 800 mg given 12 hours apart.[78] Tocilizumab on its own is a treatment for systemic JIA refractory to corticosteroid therapy.

Lenzilumab

Lenzilumab is an anti-GM-CSF monoclonal antibody effective at managing CRS by reducing myeloid cells activation and decreasing IL-1, IL-6, MCP1, MIP1 and IP-10 production.[65] Lenzilumab is efficacious and safe in the treatment of patients hospitalized for COVID-19.[79]

Rituximab

Rituximab is effective in EBV-related HLH and underlying autoimmune disorder with predominantly B cell-driven autoantibody/aberrant hypergammaglobulinaemia response (e.g. SLE). The drug depletes EBV-infected B cells. The dose of rituximab is 375 mg/m^2 weekly for 2 to 4 times.[72]

Anakinra

Anakinra is a slightly modified recombinant human IL-1 receptor antagonist protein used to treat systemic JIA/MAS, familial Mediterranean fever, cryopyrin-associated periodic syndromes and Still disease.[80–82] Anakinra is administered subcutaneously and has been used to treat patients with a cryopyrin-associated periodic syndrome, including neonatal-onset multisystem inflammatory disease.[80–82] It can be used in combination with some disease-modifying antirheumatic drugs.[80–83] The medication has also been used to treat secondary HLH in paediatric patients with other rheumatological diseases.[84] It is used off-label to treat systemic juvenile idiopathic arthritis and other autoinflammatory syndromes. Anakinra was used in 2021 to treat SARS-CoV-2 in adults with pneumonia and those developing severe respiratory failure.[85] It has been shown that patients with SARS-CoV-2 refractory to antiviral and anti-IL-6 treatment may respond favourably to treatment with the anti-IL-1 drug (anakinra 100 mg single dose, subcutaneous). Anakinra may also be effective in treating the cytokine storm associated with MAS.[54]

Rilonacept

Rilonacept (IL-1 inhibitor) has been used for the treatment of pericarditis and various conditions associated with pericarditis such as MAS.[86] The high efficacy and safety profile of rilonacept for recurrent pericarditis means it could be used as a second-line therapy ahead of or as an alternative to various corticosteroids.

Canakinumab

Canakinumab is a human monoclonal antibody targeted at IL-1β. The drug is used in the treatment of active Still disease, systemic juvenile idiopathic arthritis and cryopyrin-associated periodic syndrome[87,88] (a spectrum of autoinflammatory syndromes that includes Muckle–Wells syndrome, familial cold

autoinflammatory syndrome and neonatal-onset multisystem inflammatory disease). The FDA includes a warning for potential increased risk of serious infections as a result of IL-1 blockade.[87,88]

Conclusions

The incidence of these hyperinflammatory conditions is generally low in comparison to other disease conditions. However, the mortality is high and the hospital stay is prolonged in affected patients.[89–91] Acute and critical care physicians must be aware of these conditions for early recognition to differentiate between hyperinflammatory sequelae and the underlying infectious or autoimmune disease process in order to promptly initiate anti-inflammatory therapy. Corticosteroids are often used in the initial phrase, but various disease-specific drugs and biologics are needed in the subsequent treatment and expert management of these often-difficult conditions is crucial.

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