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Kawasaki disease: Aetiopathogenesis and therapeutic utility of intravenous immunoglobulin

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ABSTRACT

Kawasaki disease (KD) is an acute febrile childhood vasculitis, associated with the development of coronary artery abnormalities in 25–30% of untreated patients. The aetiopathogenesis is not well known but it is accepted that an undefined infectious trigger in genetically predisposed individuals results in the disease. KD is characterized by an endothelial cell injury, which could be due to abnormal cytokine production and to generation of cytotoxic antibodies against the endothelial cells. Intravenous immunoglobulin IVIG is an effective treatment in preventing the occurrence of coronary artery abnormalities in KD. Several mechanisms may explain the anti-inflammatory effects of IVIG in this disease. They include modification of the cytokine balance, and alteration on both the differentiation and the function of monocytes/macrophages, neutrophils and lymphocytes.

Contents

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1. Introduction

Kawasaki Disease (KD) is an acute childhood vasculitis that was first described by Tomasaku Kawasaki in 1967 [1]. KD is characterized by high fever, rashes, cervical lymphadenopathy, conjunctivitis, oral enanthema, and erythematous induration of the hands and feet. These symptoms resolve spontaneously within 1–3 weeks, or soon after early treatment with intravenous immunoglobulin (IVIG) and aspirin. Inflammation of medium-sized arteries throughout the body, particularly of the coronary arteries, can occur during the acute illness and can result in coronary artery aneurysms in 25–30% of untreated patients [2,3]. KD is the most common acquired heart disease in children in developed countries. Although treatment with IVIG is an effective therapy for KD, not all children respond to it, and its mechanisms of action remain not fully established [4]. Identification of the etiology of KD would greatly enhance efforts to develop a diagnostic test, to improve therapy and to prevent KD. The recent years have witnessed the emergence of interesting findings in both etiopathogenesis and therapy of KD. This review will focus on the immunologic aspects of the KD: aetiopathogenesis and immunomodulatory effects of IVIG.

2. Clinical and biological features of KD

2.1. Clinical features

KD is the most common vasculitis of infancy and the major complications of this acute febrile vasculitis are the long term cardiac consequences. While no diagnostic test is available for KD, diagnostic criteria have been established by the Japanese Ministry of Health research committee and have been adopted by the American Heart Association and the American Academy of Pediatrics [5] (Table 1).

Patients with fever at least for 5 days and who present less than 4 of the principal criteria can be diagnosed with KD when coronary artery abnormalities are detected by 2-dimensional echocardiography or angiography.

In the presence of ≥4 principal criteria, diagnosis of KD can be made on day 4 of illness [5]. Coronary artery aneurysms may progress in the sub-acute phase. In severe cases, KD leads to heart attacks, coronary artery-aneurysm rupture and/or sudden death [6,7]. 15–20% of children with KD who are febrile but have less than 4 main features may still develop coronary artery dilatation and aneurysms. They are classified as having incomplete KD, a particularly challenging diagnosis that is more common in infants under 6 months [8,9]. Serial echocardiography, performed at a center experienced in examining the coronary arteries of children, is needed for patients with acute KD. For children with an uncomplicated course, echocardiography should be repeated at two weeks and six to eight weeks after diagnosis [5].

Table 1
Clinical features of Kawasaki disease.

Fever of at least five days duration
Polymorphous exanthema
Bilateral non-exudative conjunctival injection
Changes in the oral cavity, including strawberry tongue erythematous, fissured lips and injected pharynx
Changes in the peripheral extremities, including erythema or indurative oedema and later desquamation
Cervical lymphadenopathy, often unilateral and large (≥1.5 cm)

2.2. Biological features

Laboratory findings, not specific for KD and shared by other acute inflammatory febrile diseases, are: leukocytosis with neutrophils and immature cells, elevated erythrocyte sedimentation rate (ESR), elevated C-reactive protein (CRP), anemia, abnormal plasma lipids, hypoalbuminemia, hyponatremia, thrombocytosis after week 1, sterile pyuria, elevated serum transaminases, elevated serum gamma glutamyl transpeptidase, pleocytosis of cerebrospinal fluid and leukocytosis in synovial fluid.

Predictive factors of aneurysms have been identified: male sex, age <12 months or >8 years, C-reactive protein >200 mg/dl, albumin <35 g/L, platelet count $\leq 35 \times 10^{10}$/L, delay of initiation of IVIG or lower dose of IVIG, recurrence of KD [10].

3. Aetiopathogenesis

3.1. Etiology

The cause of KD remains unknown. It is generally accepted that an undefined infectious trigger in a genetically predisposed individual results in the disease [11–14]. A genetic predisposition is suspected based on clinical and epidemiologic features. Although KD has been reported all over the world, the disease is over-expressed among Asian populations, especially Japanese [15]. The Japanese incidence (135–200/100,000, 5 years of age) is 10–15 times greater than among the Caucasians (9–17/100,000, 5 years of age) [16].

In light of an absence of association between KD and specific HLA types [17,18], Shulman et al. investigated the relationship of the distribution of immunoglobulin allotypic markers for susceptibility to KD in Japanese, Japanese-American, and white American populations. Immunoglobulin allotypes represent another system of human genetic markers. They found that in all populations studied, differences were observed between patients with KD and race-matched control subjects. White patients with KD have allotypic markers more closely resembling those of the Japanese population which has a substantially higher incidence of KD [11]. Polymorphisms in several immune genes such as IL-4, chemokine receptor 5, chemokine (C–C motif) ligand 3-like 1 and inositol phosphate kinase C, have been implicated and are compatible with an etiology that is probably infectious [19–21].

Clinical features of KD that support an infectious cause include an abrupt onset of symptoms, a resolution of the illness in 1–3 weeks, even without treatment and usually without recurrence, the young age of the group that is affected (most cases present during the first or second year of life, when susceptibility to most ubiquitous agents is highest), the winter–spring predominance of cases in non-tropical climates and the existence of epidemics and clusters of case [22].

Many possible aetiological features of agents have been suggested that include mercury, Rickettsia-like agent, *Propriobacterium acnes*, Rug shampoo, *Leptospira* spp., *Streptococcus sanguis*, Retrovirus,

Epstein-Barr virus or cytomegalovirus, toxic shock syndrome toxin 1 and other bacterial toxins, Coronavirus NL-63, Human bocavirus, and previously unrecognized persistent RNA virus. However, none of the above aetiological features has been confirmed by subsequent studies [14,23–34].

The hypothesis that a bacterial toxin causes KD is favored by some investigators. This theory is based on clinical similarities between KD and staphylococcal or streptococcal toxin-mediated illnesses, such as peeling of hands and feet, and strawberry tongue. In addition, in acute KD, many cytokines are up regulated in the serum of patients and there is over-representation of particular T-lymphocyte-receptor Vβ families in the peripheral blood [35,36].

Intracytoplasmic inclusion bodies have been identified in the ciliated bronchial epithelium of children with acute KD [37]. The presence of inclusion bodies in inflamed tissues during an acute illness such as KD is suggestive of an infection that is due to intracellular pathogens, such as virus [23]. An autoimmune mechanism of KD pathogenesis has also been proposed but the spontaneous resolution of KD and its generally non-recurring nature make this theory less plausible [38].

3.2. Immunologic aspects

KD causes a vasculitis, which is the most severe in the medium-sized arteries but pathological examination reveals that small arterioles, larger arteries, capillaries and veins are also affected to a lesser extent. The endothelial cells undergo histological changes consistent with both endothelial cell activation and endothelial cell damage. These morphologic features include enlarged endothelial cells with increased synthetic organelles, increased replication of endothelial cells, and a marked increase in the adhesion of leukocytes to the endothelial wall, endothelial cell necrosis and extracellular fibrin deposition.

Levels of a variety of inflammatory cytokines such as TNF-α, IL-1 and IL-6 are increased in serum during acute KD [39–41]. Peripheral blood mononuclear cells from patients spontaneously secrete high levels of TNF-α and IL-1 [42]. The percentage of TNF-positive cases in KD patients with coronary involvement was higher than that of patients without coronary involvement. [40]. All these findings suggest that activation of monocytes/macrophages and TNF-α activity play important roles in the pathogenesis of KD.

Furthermore, the presence of circulating cytotoxic anti-endothelial cell antibodies reactive with cytokine-induced activation antigens on vascular endothelium, has been reported [38,43,44]. Leung et al., have found that IgG and IgM antibodies in acute KD sera, cause lysis of endothelial cells stimulated with IL-1 or TNF [45,46]. Thus, there are circulating cytotoxic anti-endothelial cell antibodies reactive with cytokine-induced activation antigens on vascular endothelium.

Thanks to these observations, it has been postulated that there are at least two requirements for endothelial injury in KD: increased cytokine production, triggered by an unknown etiological agent or toxin, inducing new endothelial antigens; and the generation of cytotoxic antibodies directed to these induced endothelial antigens, possibly related to the polyclonal B-cell activation in this disease.

Infiltrating macrophages, T lymphocytes and cellular components of the arterial wall, such as myofibroblasts, are important in disease pathogenesis. They secrete a number of inflammatory mediators, enzymes and other molecules, such as vascular endothelial growth factor (VEGF), which contributes to vascular leakage and edema.

Pathological studies have demonstrated transient infiltration of neutrophils in the very early stage of acute KD before infiltration by mononuclear cells. Recent observations suggested that nitric oxide (NO) produced by neutrophils has a role in triggering the early endothelial dysfunction in KD [47]. Neutrophils in acute KD generate both NO and reactive oxygen species (ROS) considerably, while NO production is exclusive in the early stage of KD [48].

Kobayashi et al., have demonstrated that in the acute phase of KD, the expression of an adhesion molecule CD11b was significantly increased on polymorphonuclear leucocytes (PMN). In general CD11b promotes firm attachment of the PMN to the endothelium, which allows transendothelial migration into inflamed tissues. In addition, PMN generate large amounts of ROS. Therefore, enhanced expression of CD11b induced by circulating inflammatory cytokines is likely to promote adhesion and transendothelial migration of leucocytes in KD [49]. Several clinical studies have reported that activation of PMN may contribute to the severity of KD [50]. In addition, oligoclonal IgA plasma-cell infiltration has also been demonstrated in the arterial wall, the upper respiratory tract and the pancreas of patients with acute KD [51]. The presence of IgA-producing cells within the vascular wall may indicate an antigen-driven immune response to an etiologic agent with a respiratory or gastrointestinal portal of entry.

Thymically derived natural CD4+CD25+ Foxp3+ regulatory T cells (Tregs) suppress a wide variety of effector immune cells [52,53]. Several diseases have been documented to be secondary to the loss of the Treg population in mice and human [52,54,55]. Furuno et al. characterized the involvement of Tregs in KD [56]. Patients with acute phase KD exhibit a significantly lower frequency of Tregs in their peripheral blood mononuclear cells (PBMC) as compared to healthy controls. The immunologic features in peripheral blood during acute KD are summarized in the Table 2 [57]. Thus, KD is characterized by marked immune activation associated with cytotoxic anti-endothelial cell antibodies and increased cytokine production. This could contribute to the endothelial cell damage that is observed in this disease.

4. Treatment

4.1. Initial treatment

4.1.1. IVIG

Randomized controlled trials have shown that a single infusion of 2 g/kg of IVIG given 5–10 days after the onset of fever, eliminated fever in 85–90% of children within 36 h and significantly reduced the risk of coronary artery aneurysms [58,59]. Two meta-analyses have demonstrated a dose–response effect, with higher doses given a single infusion having the greatest efficacy [60]. This therapy should be instituted within the first 10 days and, if possible, within 7 days of illness. Clinical studies comparing the efficacy of IVIG products failed to find a significant difference between commercial preparations of IVIG. Even when treated with high-dose IVIG within the first 10 days of illness, 5% of children with KD develop at least transient coronary artery dilatation and 1% develops giant aneurysms.

4.1.2. Aspirin

Aspirin remains one of the mainstays of therapy because of its anti-inflammatory and anti-thrombotic actions [61]. During the acute phase of illness, aspirin is administered at anti-inflammatory doses (60 to 80 mg/kg per day in 4 doses) with IVIG. High-dose aspirin and IVIG appear to possess an additive anti-inflammatory effect. Practices regarding the duration of high-dose aspirin administration vary across institutions. When high-dose aspirin is discontinued, clinicians begin low-dose aspirin (3–5 mg/kg per day, given as a single dose).

Table 2
Immunologic features of peripheral blood during acute KD.

T lymphocytopenia
Deficiency of suppressor T cells
Increased numbers of activated helper T cells
Decreased numbers of CD4+CD25+ regulatory T cells
Polyclonal B-cell activation
Circulating antibodies against activated endothelial cell antigens
Increased cytokine (IL-1, IL-6, TNF-α) production

Low-dose aspirin has an anti-platelet effect and should be continued until six to eight weeks after disease onset if there are no coronary artery abnormalities or indefinitely if abnormalities are present.

4.2. Treatment of refractory KD

Approximately ≥10% of patients with KD fails to defervesce with initial IVIG therapy. Failure to respond usually is defined as persistent or recrudescent fever ≥36 h after completion of the initial IVIG infusion.

Abe et al. reported that polycythemia rubra vera 1, a granulocyte colony-stimulating factor levels may be good biomarker for predicting response to IVIG in patients with KD [62]. Egami et al. generated a prediction score of resistance to IVIG [63]. They assigned 1 point for infants younger than 6 months, before 4 days of illness, platelet count $\leq 30\times10^{10}$/L, and CRP≥8 mg/dl. 2 points were assigned for alanine aminotransferase≥80 IU/L. Using a cut-off point of 3 and more with this prediction score, they could identify the IVIG-resistant group with 78% sensitivity and 76% specificity.

Ogata et al. investigated the transcript abundance in the leukocytes of IVIG-responsive patients (group A) and IVIG-resistant patients (group B) using a microarray analysis before treatment [64]. The IVIG-responsive (group A) and IVIG-resistant patients (group B) were predicted before starting the initial treatment using the Egami scoring system and randomly allocated as a single-IVIG treatment group (group B1) or as a IVIG-plus-methylprednisolone (IVMP) combined therapy group (group B2). The transcripts related to IVIG resistance and to the development of coronary artery lesions, such as IL1R, IL18R, oncostatin M, suppressor of cytokine signaling-3, S100A12 protein, carcinoembryonic antigen-related cell adhesion molecule-1, matrix metallopeptidase-9, and polycythemia rubra vera-1, were more abundant in group B patients in comparison with group A patients.

The risk for coronary artery aneurysms is increased in refractory KD patients and no controlled clinical trials have established their optimal management.

Because controlled data are lacking, the relative roles of repeated doses of IVIG, corticosteroids, TNF-α antagonists [59,65], abciximab, cytotoxic agents such as methotrexate, cyclophosphamide and cyclosporine A, and plasma exchange for patients with refractory KD remain uncertain.

4.2.1. IVIG

The American Heart Association guidelines recommend a further dose of IVIG, 2 g/kg, in children who remain febrile 36 h after the first dose of immunoglobulin [5].

4.2.2. Corticosteroids

Studies have shown that corticosteroids reduce fever [66,67]. The effects of steroids on coronary artery abnormalities are still uncertain. It is recommended that steroid treatment should be restricted to children in whom ≥2 infusions of IVIG have not been effective in alleviating fever and acute inflammation. But recently, Furukawa et al. suggested that corticosteroids may be used with comparable efficacy to a second dose of IVIG for children who fail to respond to the first dose [68]. The most commonly used steroid regimen is intravenous pulse methyl prednisolone, 30 mg/kg for 2 to 3 h, administered once daily for 1 to 3 days.

4.2.3. Infliximab (Remicade®)

In one retrospective study of 17 children with IVIG-resistant KD, infliximab, a humanized monoclonal antibody against TNF-α, was used successfully at the dose of 5–10 mg/kg with abrupt defervescence in 13/16 febrile patients, with no infusion reactions. Twelve patients had coronary abnormalities before infliximab therapy; four had transient dilatation that resolved post-infliximab infusion, three had aneurysms, and five had ectasia [69]. A phase 2 clinical trial including 16 subjects receiving infliximab has demonstrated that this treatment was safe and well tolerated in patients resistant to IVIG [70].

4.2.4. Abciximab (Reopro®)

Abciximab, a monoclonal platelet glycoprotein IIb/IIIa receptor inhibitor, has been used to treat patients in the acute or sub-acute phase of KD who have large coronary aneurysms [71]. Patients who received abciximab plus standard therapy as compared with historical controls treated with standard therapy alone showed a greater regression in maximum aneurysm diameter, suggesting that treatment with abciximab might promote vascular remodeling. Prospective controlled trials are needed.

4.2.5. Cytotoxic agents

4.2.5.1. Methotrexate. Seventeen patients with KD who had persistent fever or recrudescent fever after treatment with IVIG were given methotrexate. Low-dose oral methotrexate treatment resulted in quick resolution of fever and rapid improvment of inflammation markers without causing any adverse effects [72].

4.2.5.2. Cyclophosphamide. Wallace et al. treated 2 patients resistant to 2 doses of IVIG with intravenous cyclophosphamide and there was no progression of coronary aneurysms and no death [73].

4.2.5.3. Cyclosporin A. Kuijpers et al. reported in a case report that cyclosporin A was ineffective in halting the progression of obliterative panarteritis of a boy with a fatal KD [74].

4.2.6. Plasma exchange

Plasma exchange has been reported in an uncontrolled clinical trial to be an effective therapy in patients who are refractory to IVIG and to lower the incidence of coronary artery aneurysms [75]. Because of its risks, plasma exchange is not generally recommended.

These therapies have been used in small numbers of patients, and data are too limited for official recommendations.

4.3. Treatment of coronary abnormalities

The acute management of patients with coronary artery abnormalities depends on the extent and severity of the lesions. Although low-dose aspirin is adequate for patients with mild disease (dilatation, small, stable aneurysm), additional therapy such as anti-platelet agents and heparin may be required for patients with more severe disease because of the increased risk of thrombosis from the abnormal blood flow through coronary aneurysms. Most patients with large or giant coronary artery aneurysms (internal diameter greater than 8 mm) are maintained on aspirin (or clopidogrel) and warfarin to prevent thrombosis within the aneurysm and myocardial infarction [5].

5. Mechanisms of action of IVIG

IVIG is a polyspecific immunoglobulin IgG preparation purified from plasma pools of several thousand healthy donors [76–78]. IVIG is a safe preparation with no long term side effects [76,79]. IVIG was initially used as substitutive treatment for patients with immunodeficiencies and subsequently used for treatment of a wide range of autoimmune and systemic inflammatory diseases [59,80–84].

In KD, IVIG was first reported by Furusho et al. in 1984 to effectively reduce the incidence of coronary artery lesions [85]. Although treatment with IVIG is an effective therapy for KD, their precise mechanisms of action are not fully understood. Clinically IVIG reduces the prevalence of coronary artery abnormalities by reducing the tissue inflammation and the immune activation. Some potential

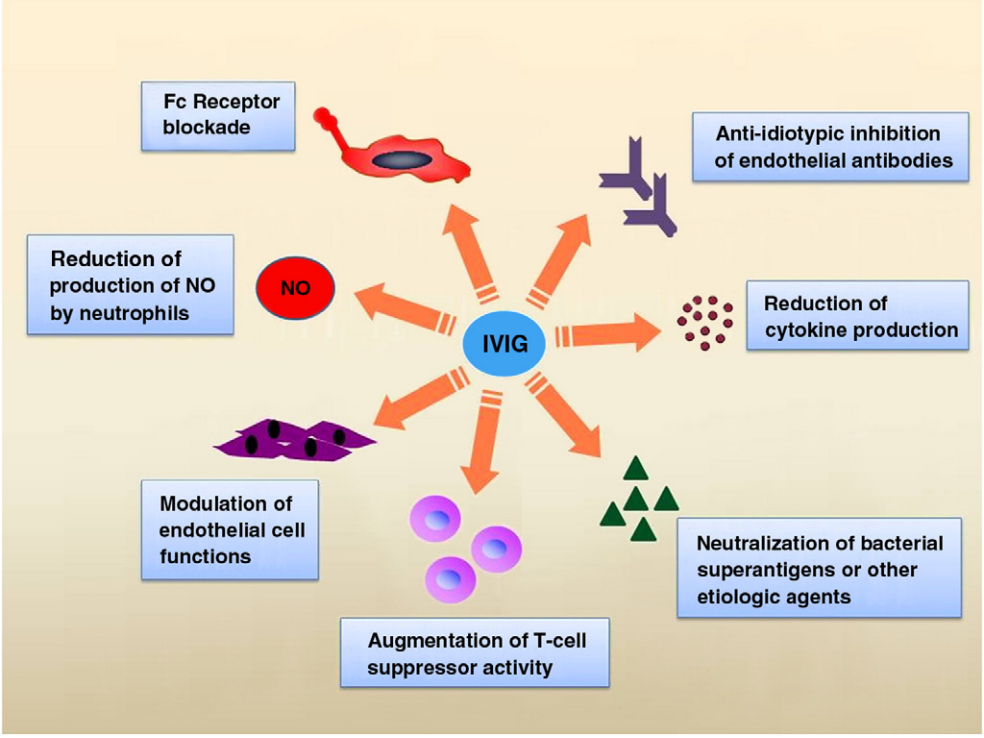

Fig. 1. A schematic representation of the proposed mechanisms of action of IVIG in Kawasaki disease.

mechanisms of action of IVIG are summarized in Fig. 1 and Table 3 [76–78,86–89].

5.1. Modulation of endothelial cell function

We have shown that IVIG inhibits endothelial cell proliferation in a dose- and time-dependant manner. IVIG has also down-regulated TNF-α or IL-1β-induced expression of mRNA encoding major adhesion molecules (ICAM-1 and VCAM-1), chemokines (MCP-1, M-CSF, GM-CSF), and pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6), which are significantly implicated in the leukocyte recruitment observed in KD [90]. As the endothelium plays a central role in the immunopathology of KD, it is likely that IVIG exerts its beneficial effect through the modulation of endothelial cell functions.

5.2. Inhibition of cell adhesion

Integrins are a major group of adhesion molecules that serve both adherence and signaling functions. Integrins play a critical role in the cell differentiation and embryogenic development, inflammation and immune responses. Many of the integrins share affinity towards the RGD recognition sequence (the Arg-Gly-Asp motif) in their extracellular matrix ligand and are able to discriminate between different RGD-containing proteins. We have shown that IVIG contains antibodies that bind to human RGD-containing integrin ligands [91]. The biological relevance of anti-RGD antibodies in IVIG was demonstrated by their ability to inhibit B-lymphocyte adhesion to fibronectin. The presence of natural IgG antibodies to the RGD motif may contribute to the immunomodulatory and anti-inflammatory effects of IVIG in KD.

Table 3
Proposed mechanisms of action of IVIG in Kawasaki disease.

Modulation of endothelial cell functions
Inhibition of cell adhesion
Anti-idiotypic inhibition of anti-endothelial antibodies
Anti-NGF effect
Reduction of inflammatory cytokine production
Inhibition of cytokine-induced endothelial cell activation
Fc receptor blockade
Suppression of antibody synthesis
Reduction of production of NO by neutrophils
Augmentation of T-cell suppressor activity
Neutralization of bacterial superantigens or other etiologic agents

5.3. Anti-idiotypic inhibition of endothelial antibodies

IVIG contains anti-idiotypic antibodies that can directly inhibit the binding of several disease-associated autoantibodies to their targets. For instance, IVIG has been shown to contain anti-idiotypic antibodies that neutralize anti-factor VIII antibodies in patients with hemophilia, ANCA in vasculitis, anti-acetylcholine receptor autoantibodies in patients with myastheneia gravis [76]. Nevertheless, in 1989, Leung et al. demonstrated that IVIG does not reduce cytotoxic antibody against endothelial cells in six patients tested [42]. Furthermore, studies of blood and skin biopsies obtained from acute KS patients, prior to and after treatment with IVIG indicate that IVIG treatment does not reduce serum cytotoxic anti-endothelial cell antibody activity [42].

5.4. Effect of anti-NGF antibodies

Nerve growth factor (NGF), a neurotrophin, is a regulator of development, survival and function of neuronal and non-neuronal cells. It may play a role in many inflammatory diseases due to its ability to stimulate the release of inflammatory neuropeptides. During the acute phase of KD, serum levels of NGF are elevated [92]. The studies of Warrington et al. showed that anti-NGF antibodies are present in IVIG and the authors have suggested that the therapeutic effect of IVIG may lie in the anti-NGF component of the IVIG [93].

5.5. Reduction of inflammatory cytokine production

IVIG can modulate the production of cytokines to exert anti-inflammatory effects [76]. In responsive patients, the serum levels of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) are decreased after IVIG therapy [42,94]. These findings indicate that the effects of IVIG in KD are mediated mainly by robust suppression of activated immune cells in the peripheral circulation. IL-6 may play a role in the acute systemic inflammatory response of KD and the majority of symptoms of this disease are attenuated by the decrease in IL-6 with IVIG therapy [94]. Using a murine model of KD, Lau et al. have recently shown that IVIG can inhibit lymphocyte activation and production of TNF-α [95]. But they have also shown that IVIG has no effect on TNF-α-mediated matrix metalloproteinase 9 (MMP-9) activity. In this murine model of KD, TNF-α-mediated MMP-9 activity has a critical role in the development of coronary artery elastin breakdown.

5.6. Modulation of monocytes and macrophages

Ichiyama et al. demonstrated that IVIG inhibits TNF-α-induced NF-κB activation in monocytes/macrophages [96]. NF-κB is a transcription factor for genes that encode pro-inflammatory cytokines, chemokines and adhesion molecules that mediate inflammation.

By examining gene expression profiles of PBMC and purified monocytes from patients with acute KD, before and after IVIG therapy, Abe et al. inferred that IVIG suppresses an array of immune activation genes in monocytes, including activating FcγRs and the S100A8/A9 heterocomplex (this complex has been shown to enhance monocyte adhesion to endothelial cells and to cause neutrophil chemotaxis). The expression of FcγRI and FcγRIII on monocytes were reduced following IVIG therapy [96,97]. Interestingly, it has been demonstrated that IVIG therapy in patients with KD did not increase the expression of the inhibitory Fc receptor FcγRIIB in peripheral blood CD14+ monocytes/macrophages during the acute stage [98].

5.7. Reduction of production of NO by neutrophils

Takatsuki et al. evaluated the oxidative stress during acute phase of KD by measuring urinary 8-iso-prostaglandin F2α (8-iso-PG). Indeed, measurement of the urinary excretion of 8-iso-PG has been shown to reflect enhanced oxidative stress. They have demonstrated that IVIG reduces vascular oxidative stress in patients with KD [99]. The amount of NO produced by neutrophils decreased after IVIG treatment, while there was no significant change in ROS production [48]. This is important because NO has a role in triggering the early endothelial dysfunction in KD [47].

5.8. Regulation of T and B cells

Leung et al. shown that IVIG treatment in KD causes a significant reduction in the number of antibody-producing B cells [100]. The authors have further reported that IVIG leads to a significant increase in circulating suppressor T cells and a significant reduction of activated helper T cells [100].

6. Conclusion

KD is an important cause of fever in young children and is a common cause of acquired heart disease. It is characterized by immune activation and increased cytokine production. Recent observations have allowed a better understanding of the pathogenic events: KD could be an infectious disease in genetically predisposed individuals. By determining the causative agent, we could improve diagnosis, therapy and prevention of KD. IVIG reduces the prevalence of coronary artery abnormalities by reducing the immune activation. Further clarification of the mechanisms of action of IVIG in KD should provide insights into the pathogenesis and/or the etiology and help conceiving more targeted therapeutic strategies of this disorder.

Take-home messages

- Kawasaki disease is a pediatric vasculitis associated with the development of coronary artery abnormalities in 25–30% of untreated patients.
- Epidemiological and immunological features suggest the role in the pathogenesis of KD of an intracellular pathogen such a virus in a genetically susceptible host.
- The endothelial injury in KD is due to increased cytokine production and the generation of cytotoxic antibodies against the endothelial cells.
- IVIG is the mainstay of treatment of KD, and has markedly reduced the incidence of coronary artery abnormalities.
- Ten percent of patients with KD fail to defervesce with initial IVIG therapy.
- The mode of action of IVIG in KD is not fully understood although several mutually non-exclusive mechanisms have been proposed: they involve effect on endothelial cells, macrophages and monocytes, neutrophils and T and B cells, expression of adhesion molecules and cytokine production.

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The tolerogenic peptide hCDR1 downregulates pathogenic cytokines and apoptosis and upregulates immunosuppressive molecules and regulatory T cells in peripheral blood mononuclear cells of lupus patients

A tolerogenic peptide, hCDR1, ameliorated murine lupus via the upregulation of functional regulatory cells and by immunomodulating cytokine production. In the present study, **Sthoeger ZM. et al. (Hum Immunol 2009; 70:139-45)** analyzed the ability of hCDR1 to similarly affect gene expression and regulatory T cells when incubated with peripheral blood mononuclear cells (PBMC) of lupus patients. T this end, peripheral blood mononuclear cells (PBMC) of 11 lupus patients and five gender-and age-matched healthy controls were cultured with hCDR1 or a control peptide. Gene expression and regulatory T-cells were assessed. hCDR1 significantly downregulated interleukin (IL-1 beta) interferon (IFN-gamma), and IL-10 gene expression. Furthermore, hCDh1 upregulated the expression of the anti-apoptotic Bcl-xL molecule and downregulated the pro-apoptotic caspase-3, resulting in reduced rates of apoptosis. hCDR1 increased the expression of transforming growth factor (TGF)-betta, FoxP3 and the negative regulators Foxj1 and Foxo3a. No significant effects were observed using a control peptide or when PBMC of healthy donors were incubated with hCDR1. The elevated gene expression of FoxP3 was due to hCDR-induced upregulation of TGF-betta, resulting in an increase of CD4+CD25+FoxP3+ functional, regulatory cells. The ability of the regulatory cells to diminish IFN-gamma expression and to upregulateTGF-beta was abrogated after the addition of neutralizing anti-CD25 antibody, confirming their role in the beneficial effects of hCDR1.

Decrease in phenotype regulatory T cells in subsets of patients with common variable immunodeficiency

Common variable immunodeficiencies (CVID) are a heterogeneous group of antibody deficiency disorders complicated by autoimmune, lymphoproliferative and/or granulomatous manifestations, suggesting variations in immunoregulation. In this study, **Horn J. et al. (Clin Exp Immunol 2009; 156: 446-54)** sought to quantify regulatory CD4 T cells (Treg) in the blood of CVID patients and to correlate the frequency with clinical manifestations and classification subgroups. Blood samples from 99 CVID patients in Freiburg, London and Sydney, who had been phenotyped clinically and stratified according to their memory B cell phenotype, were analyzed for the proportion of Treg cells, defined either as CD25+/FoxP3+, CD25+/CD127low/FoxP3+ or CD25+/CD127low/CD4+ T cells, and results compared with 49 healthy controls. Irrespective of the phenotype used to define them, there was a significant decrease in the Treg cell proportion in patients with granulomatous disease and immune cytopenias. This allowed the definition of a subgroup of CVID patients with abnormally low Treg cells, which had a higher rate of these two manifestations as well as autoimmune diseases in general. There was also a significant reduction in the proportion of Treg cells in the Freiburg group compared with other CVID patients and controls, but there were no differences between the Paris groups. The reduction in Treg cells in subsets of CVID patients may be relevant to their clinical manifestations, and may contribute to our understanding of the pathogenesis of CVID complications.