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The Treatment Strategies for Kawasaki Disease without Response to Intravenous Immunoglobulin (IVIG)

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Abstract:

Background: Kawasaki Disease (KD) is an acute vasculitis that occurs predominantly in children. The standard treatment is initial therapy with intravenous immunoglobulin (IVIG), but some patients develop resistance to IVIG, which increases their risk of developing coronary artery lesions. This review aims to analyze and summarize the causes and pathological mechanisms of IVIG resistance, as well as other treatment strategies. *Results:* Studies have found that IVIG resistance is mediated by multiple factors including genetic susceptibility, immune dysregulation, and changes in vascular endothelial cell characteristics, with persistently elevated pro-inflammatory cytokines as the core manifestation. Second-dose IVIG, glucocorticoids, and infliximab as second-line treatments each have their advantages and disadvantages. A second IVIG dose is currently the preferred treatment for IVIG non-responders in KD, while infliximab is more effective in controlling fever and coronary inflammation. Combination therapy may be a better option. However, existing predictive models remain limited, with obvious heterogeneity in clinical data. *Conclusion:* The pathogenesis of Kawasaki disease remains unclear. Current treatment options still carry risks and controversies. Further experimental research is needed to elucidate resistance mechanisms, construct predictive models, conduct heterogeneous experiments, and promote international collaboration to achieve breakthroughs in the treatment of this disease.

Keywords: Kawasaki disease; IVIG resistance; treatment strategies; vasculitis.

1. Introduction

Kawasaki disease (KD) is an acute, self-limited vasculitis primarily affecting children aged under 5 years. Its clinical manifestations mainly include persistent fever, bilateral conjunctival congestion, red, swollen, and chapped lips, polymorphous rash, redness and swelling of the extremities, and enlarged cervical lymph nodes. First reported by Japanese scholar Tomisaku Kawasaki in 1967, KD has now become one of the most common causes of acquired heart disease in children. The core of its treatment lies in controlling systemic inflammation during the acute phase to prevent coronary artery lesions (CAL) and their long-term cardiovascular complications [1]. Since the 1980s, high-dose intravenous immunoglobulin (IVIG) combined with aspirin has become the standard initial treatment regimen for KD. This has reduced the incidence of coronary artery lesions (CAL) from 20%–25% to 3%–5% [2]. However, approximately 10% to 20% of children do not respond to initial IVIG treatment, manifesting as persistent or recurrent fever, known as "IVIG resistance" [3]. These children have a significantly increased risk of developing coronary artery dilatation or aneurysms, making it a key and challenging issue of clinical management for KD [4]. This article systematically reviews the mechanisms underlying the development of IVIG resistance, compares the efficacy and safety of different second-line treatment options, explores the current challenges faced by researchers, and discusses future directions for development. It aims to be a resource for clinical decision making and future research efforts. However, current standardized IVIG regimens do not account for the heterogeneity of treatment resistance.Three key pathways contribute to IVIG resistance, including pyroptosis, endothelial inflammation and gut immune imbalance. Conventional indicators cannot reflect core pathogenic differences.Different resistant subtypes respond to distinct targeted drugs.Specific biomarkers can screen patient subtypes accurately. This stratified matching strategy provides a new reference for individualized refractory disease treatment.

2. Clinical manifestations, pathogenesis, and IVIG resistance mechanism of the KD

2.1 Diagnostic Criteria and Clinical Features

The Kawasaki Disease Research Committee in Japan established the world's first diagnostic criteria for KD, which are still widely adopted to this day [5]. According to these criteria, diagnosis requires persistent fever for at least 5 days and the presence of at least 4 out of the following 5 clinical symptoms: 1. Bilateral conjunctival congestion (without exudation);2. Polymorphic rash;3. Oropharyngeal changes, including lips congestion, cracking, pharyngeal congestion, and strawberry tongue (a tongue that is red and swollen like a strawberry);4. Limb changes, including hand and foot edema, erythema on the palms and soles of the feet, and perifungal desquamation that appears during the recovery phase; 5. Cervical lymph node enlargement can reach a diameter over 1.5 cm.

2.2 Mechanisms of IVIG Resistance Genetic Susceptibility

Multiple kinds of factors and signaling pathways work together to trigger IVIG resistance occurring in Kawasaki disease, which is closely related to the disorder of innate immunity and adaptive immunity. Vascular endothelial cell property alteration, gut flora dysbiosis and genetic susceptibility also serve as vital influencing factors. All above mechanisms interact mutually, further accelerating the occurrence and progression of drug resistance.

2.2.1 Genetic susceptibility

Genetic background acts as the core internal inducement for children suffering KD to develop IVIG resistance. Owing to unique genetic mutation characteristics, East Asian groups show far higher morbidity and drug resistance rate of KD compared with other races. Various gene polymorphisms take part in the formation of resistance phenotype by modulating immune activation, inflammatory reaction and cell apoptosis. The negative controlling effect on T cell activation will be weakened by mutation of ITPKC and FCGR2A genes, meanwhile the clearance efficiency of immune complex will also decline. Relevant latest studies have proven that single nucleotide polymorphism of Rab31 gene is able to dramatically downregulate Rab31 protein expression. Low expressed Rab31 cannot suppress the assembly and activation of NLRP3 inflammasome effectively, thus driving massive release of downstream pro-inflammatory cytokines including IL-1β and IL-18 [6,7].

2.2.2 Immune dysregulation and inflammatory storm

The unbalanced state of immune activation and inflammation acts as the key motivation for KD patients to produce IVIG resistance, which covers various abnormal performances of dual immune systems. The mutual interaction between innate immunity and adaptive immunity gives

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rise to severe inflammatory storm inside body, which greatly hinders the treatment effect of IVIG. This dysregulated crosstalk amplifies cytokine release, disrupts B-cell tolerance, and impairs Fcγ receptor-mediated clearance of immune complexes—further diminishing IVIG's anti-inflammatory and immunomodulatory actions.

From the perspective of innate immunity, neutrophils of sick children maintain persistent hyperactivation. Massive NETs are produced together with plenty of inflammatory mediators.Monocytes keep activating inflammatory reaction continuously relying on S100A12-TLR4-MYD88 signaling axis.

2.2.3 Vascular endothelial injury

Evidence suggests that in patients who do not respond to IVIG, PTX3 levels rise markedly. This elevation promotes vascular endothelial injury through activation of the NFκB pathway. On the adaptive immunity side, an imbalance occurs between effector cells and regulatory cells: $CD8^+$ T cells and Th17 cells expand abnormally, while the number and function of immunosuppressive regulatory T cells (Tregs) decline [8,9]. Such immune dysregulation not only fuels the inflammatory cascade but also makes the child's immune cells largely refractory to the modulating effects of IVIG [8].

In another line of investigation, researchers built a Kawasaki disease model using induced pluripotent stem cells (iPSCs). They observed that in vascular endothelial cells taken from IVIGresistant children, the expression of the chemokine CXCL12 and components of the IL6 pathway was significantly upregulated. This further amplifies the inflammatory response within the vascular endothelium.

2.2.4 Gut microbiota imbalance

Gut microbiota imbalance is another important external factor contributing to IVIG resistance in KD. It can compromise the integrity of the intestinal barrier, thereby trigger systemic inflammation and ultimately interfering with the therapeutic efficacy of IVIG [10].

In summary, IVIG resistance arises from multiple interacting factors. Genetic predisposition—such as the high disease incidence and resistance rate seen in East Asian populations—leads to weakened immune regulation due to gene mutations. Immune disorders, particularly excessive innate immune activation and impaired Treg function, serve as the core drivers. These are further amplified by heightened vascular endothelial inflammation and gut microecological imbalance. Together, these factors cooperatively shape the resistant phenotype.

3. Treatment strategies and Mechanism Comparison for KD without Response to IVIG

3.1 Definition of IVIG Resistance

In some children with Kawasaki disease, resistance to intravenous immunoglobulin (IVIG) may occur during treatment. The typical criterion for resistance is as follows: if a child still has a fever (temperature >38°C) 36 hours after receiving the initial IVIG infusion, and inflammatory markers such as CRP and ESR fail to decreaseor even risewhile clinical signs like rash and lymphadenopathy persist, a second dose of IVIG is usually administered [3].

3.2 Mechanism of Action of IVIG

In such resistant patients, proinflammatory cytokine levels remain high. One of the mechanisms of IVIG is to compete with Fcγ receptors on monocytes, thereby downregulating the TLR4 signaling pathway and reducing proinflammatory cytokines such as TNFα and IL1β. At the same time, IVIG inhibits abnormal platelet activation and reduces hypercoagulability. In other words, it works through both immune regulation and vascular protection to prevent the progression of coronary artery disease [2].

3.3 Second Dose of IVIG

A second dose of IVIG has an additional effect: promoting regulatory Tcell proliferation and activation, enhancing immune tolerance, and reducing autoimmune attacks. It also inhibits neutrophil chemotaxis and adhesion, which helps limit inflammatory infiltration and tissue damage in the vascular wall. Together, these mechanisms lower the risk of cardiovascular complications. That said, if a second dose still fails, other options such as glucocorticoids or infliximab should be considered [11,12].

4. Comparison of Different Treatment Strategies

When IVIG resistance occurs during KD treatment, a second dose of IVIG can quickly reduce inflammation, relieve symptoms, and lower the risk of coronary artery damage. Still, the resistance rate remains 10%–20%, and adverse reactions such as anaphylaxis and hemolysis are possible [3].

4.1 Glucocorticoids

Glucocorticoids are another option. They bring inflammatory markers down rapidly. The RAISE study showed that combining IVIG with prednisone significantly reduced coronary artery abnormalities in highrisk pediatric patients [13]. The main drawback is side effects-for example, increased neuroexcitability (crying, irritability), which goes away after stopping the drug. The study did not report other adverse reactions like anaphylaxis.

4.2 Infliximab

Infliximab represents a third strategy. In patients resistant to IVIG, it works quickly, effectively controls coronary inflammation, and leads to shorter hospital stays and lower costs compared to repeated IVIG infusions [14]. The KIDCARE trial found that infliximab achieved faster fever resolution and shorter hospitalization than a second dose of IVIG, with a lower incidence of severe anemia [15].
However, it is associated with infusion reactions, infections, injection site reactions, neutropenia, hepatitis, and malignancies as potential drawbacks.

4.3 Second IVIG vs. Infliximab

The above three regimens have shown certain clinical efficacy for refractory KD in the re-treatment of KD. However, research has revealed that the use of glucocorticoids in patients with acute KD may induce exacerbation of aneurysms and vascular remodeling dysfunction. According to the report [13], glucocorticoids are primarily recommended for children with persistent fever who fail to respond to at least two courses of IVIG therapy, and have undergone ≥ two IVIG treatments. The second dose of IVIG and Infliximab, as the main treatment options, showed no significant difference in anti-inflammatory and treatment resistance effects. However, since IVIG does not pose risks of infection, liver injury, or neutropenia related to biological agents, it is more suitable for use in children during the acute phase. It has a broad-spectrum immune regulatory mechanism and can cover multiple key resistance pathways such as Fcγ receptor blockade, regulatory T-cell recovery, and endothelial protection; However, Infliximab only targets TNF α and has a narrow anti-inflammatory spectrum. The second dose of IVIG, as an enhanced regimen for standard initial treatment, conforms to the logic of tiered therapy, has a higher level of evidence-based support, and has been unanimously recommended by authoritative guidelines such as the American Heart Association (AHA). Therefore, IVIG is still the preferred treatment measure [10].
The specific choice should be comprehensively evaluated based on the age of the child, severity of the disease, comorbidities, and the possibility of adverse reactions.

4.4 Other Biologic Agents and Combination Therapies

Several optimal clinical treatment options for managing IVIG-resistant cases have been proposed, including a second IVIG infusion alone or in combination with corticosteroids, long-term corticosteroid injections alone, or infliximab plus pulse therapy [12]. In recent years, tocilizumab, as an IL-6 receptor antagonist, has shown potential in the treatment of IVIG-resistant KD. A retrospective study involving five IVIG-resistant patients showed that tocilizumab can effectively control systemic inflammation and improve coronary artery outcomes, with no related adverse events reported in all patients after treatment [16]. These combination regimens offer new insights and optimistic prospects for KD treatment, and more effective combination treatment options still need to be explored through large-scale, high-quality experiments in the future.

5. Challenges and Future Directions in the Treatment of IVIG-Resistant KD

5.1 Heterogeneity in Clinical Data and Definition of Resistance

Current research on IVIG-nonresponsive KD still faces multiple practical challenges. The core challenges lie in the high heterogeneity of clinical data, the insufficient efficacy of prediction tools, and the poor translation and integration from laboratory research to clinical practice, among other aspects [1].
Firstly, Due to geographical and ethnic differences, the incidence of IVIG resistance is markedly higher in East Asian children but rare in European and American populations. This creates inherent limitations in patient recruitment for conducting large-scale, prospective, multicenter clinical trials [6]. Currently, the majority of evidence is derived from retrospective analyses with relatively homogeneous data sources. Meanwhile, experts have not reached sufficient consensus on the criteria for defining IVIG resistance, including the threshold for persistent fever, standards for fever resolution, selection of laboratory markers, and follow-up duration, which restricts the comparability and integration of data across different studies. Although the 2024 Updated Scientific Statement on the

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Diagnosis and Management of KD issued by the American Heart Association (AHA) put forward more intensive recommendations for follow-up intervals in high-risk patients-shortening the first post-discharge follow-up from 1-2 weeks (recommended in the 2017 version) to 1 week to enable early detection of coronary artery aneurysm formation and progression-existing evidence remains insufficient to establish unified, quantitative standards for long-term stratified follow-up protocols across different risk levels [10].

5.2 Limitations of Current Predictive Tools

Secondly, the predictive tools currently available in clinical practice still have significant performance shortcomings. Although risk scoring models such as Kobayashi and Egami, developed successively by Japanese scholars, have certain predictive value in the local population, their sensitivity and specificity decrease significantly when applied to other ethnic groups (including some Asian populations and Caucasians), limiting their clinical applicability [17]. In recent years, researchers have begun to explore new prediction models based on machine learning, integrating immune-inflammatory indicators such as the neutrophil-to-lymphocyte ratio (NLR), T-cell subsets, and cytokines, in order to improve prediction performance. A study including 282 KD patients confirmed that dynamic monitoring of routine blood parameters (NLR, PLR, MPVLR) can effectively predict IVIG resistance, and the constructed prediction model has an AUC of up to 0. 949. At the same time, body temperature monitoring has also been proven to be a simple and effective predictive indicator. A minimum body temperature below 36. 05℃ is significantly associated with IVIG sensitivity, with a specificity of up to 79. 1% [18]. In addition, metabolomics studies have found differential expression of various acylcarnitines and amino acid metabolic pathways in IVIG-resistant patients, providing new biomarkers for the construction of predictive models [19].

5.3 Complexity of Resistance Mechanisms

In addition, the complexity of resistance mechanisms further exacerbates the difficulty of research. At the genetic level, in addition to known susceptibility genes such as ITPKC and FCGR2A, Japanese researchers identified a low-frequency single nucleotide variant rs563535954 in the 3'-untranslated region of the IL4R gene. This locus is significantly associated with non-response to IVIG, and carriers are often misjudged as low-risk by existing scoring systems, suggesting that clinical indicators are still insufficient to fully elucidate the genetic susceptibility background. At the immune level, some drug-resistant children show signs of immune homeostasis imbalance, such as a decrease in regulatory T-cells (e. g., CD4 CD25 FOXP3 Treg cells), even before treatment [8]. At the level of inflammation regulation, the expression differences of the key molecule CASP1 in the pyroptosis pathway provide a new perspective for drug resistance identification [11]. In summary, the complex interaction between clinical manifestations and underlying mechanisms has not yet been clarified, and thus early identification of high-risk individuals and formulation of individualized intervention strategies still pose significant challenges.

5.4 Resistance Subtype Stratification Hypothesis

Current second-line IVIG regimens combined with hormones or infliximab are designed based on homogeneous resistance characteristics and fail to reflect disease heterogeneity. Three major pathogenic axes mediate IVIG resistance.The downregulation of Rab31 activates the NLRP3/caspase-1 pathway and increases the secretion of IL-1β and IL-18, thereby promoting pyroptosis. Elevated CXCL12 and IL-6 trigger NF-κB activation and reduce IVIG therapeutic effects. Intestinal microbiota dysbiosis decreases Treg levels and elevates Th17 responses, leading to immune imbalance. Routine indicators including body temperature, CRP and NLR cannot distinguish the dominant pathogenic axis, which reduces the population applicability of existing predictive models.A pathway-medication matching hypothesis is proposed. Treatment failure after second-line IVIG is primarily attributed to unblocked core pathogenic axes. Pyroptosis-dominated resistance matches tocilizumab intervention. Endothelial axis dysfunction is suitable for infliximab treatment. Gut immune disorder-related resistance can be targeted with cyclosporine A.Corresponding biomarkers support accurate subtype stratification. The IL-1β/IL-18 ratio and caspase-1 activity reflect pyroptosis activity. Soluble IL-6R and CXCL12 represent endothelial inflammatory status. Fecal short-chain fatty acids and peripheral Treg/Th17 ratio indicate gut immune homeostasis. Patients can be stratified into different second-line treatment groups, including IVIG, infliximab, tocilizumab and cyclosporine A. Primary endpoints include fever remission within 72 hours and stable coronary artery Z-scores.

6. Conclusion

In summary, the mechanism of KD has not been fully elucidated to date, and it is generally believed in the academic community that it may be triggered by infections in genetically susceptible individuals in genetically susceptible hosts. The unknown cause directly limits the development of treatment strategies targeting core pathways. Regarding the clinical challenge of IVIG resistance, although a stepwise or combination treatment regimen centered on a second dose of IVIG, glucocorticoids, and TNF-αinhibitors such as infliximab (IFX) has currently been established, there are still many controversies concerning the specific choice of strategy, timing of administration, and combination methods. Some high-risk children still show resistance even after receiving initial intensive treatment with IVIG combined with methylprednisolone, and their prognosis is related to indicators such as total bilirubin (total bilirubin) levels, Yang score, and IL-6 concentration, suggesting that KD in this subgroup of children may involve more complex pathological mechanisms and urgently requires more precise risk stratification and intervention strategies.

Future research can be further advanced in the following directions: firstly, strengthening basic mechanism studies, using cutting-edge technologies such as single-cell sequencing and spatial transcriptomics to thoroughly analyze key immune subsets and signaling pathways related to IVIG resistance (such as the IL-1β/IL-6 axis and the S100A-TLR4 pathway), laying a theoretical foundation for the development of new drug targets. Second, promote the upgrade of predictive systems and the optimization of personalized treatment strategies, break through the functional boundaries of existing clinical scores, integrate genetic variations (such as IL4R, ITPKC, Rab31, etc.), circulating protein biomarkers, and immune cell functional profiles, and build multimodal composite predictive models to improve the early identification capability of high-risk populations. Third, conduct well-designed prospective randomized controlled trials to systematically compare the efficacy and safety of different second-line treatment regimens (such as infliximab, glucocorticoids, cyclosporine A, etc.) in specific drug-resistant subgroups, and explore the optimal timing and combination strategies for combined therapy. Fourthly, in view of the significant racial differences in KD patients, efforts should be actively made to promote multinational multicenter collaboration and establish large clinical cohorts covering diverse ethnic backgrounds, in order to verify the reproducibility of new biomarkers across universal genetic populations. This in turn, may aid future development of more robust international consensus in the field of KD. Though IVIG resistant KD management has come a long way, prior efforts have relied more on trial and error. Current and future efforts to advance KD management aims to promote a shift towards cutting edge strategies including precision methods centered on molecular subtyping.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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