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Review

Clinical advancements of biologic agents in the treatment of Kawasaki disease based on its pathogenesis

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Abstract: Kawasaki disease (KD), also known as mucocutaneous lymph node syndrome, is an acute febrile systemic vasculitis predominantly affecting children under the age of 5 years. The hallmark of KD is systemic vasculitis, which can lead to coronary artery complications if not promptly treated. Approximately 15%–20% of untreated cases develop coronary artery aneurysms, coronary artery stenosis, or thrombosis, posing significant risks to pediatric health and survival. In recent years, the incidence of KD has shown an upward trend. While intravenous immunoglobulin in combination with aspirin remains the standard first-line therapy for acute KD, some patients exhibit resistance to intravenous immunoglobulin or progress to refractory KD. The rapid advancement of modern biomedicine has led to increased interest in biological agents for KD treatment, yielding promising outcomes.

Keywords: biological agents; Kawasaki disease; treatment; clinical progress; pathogenesis

1. Introduction

Kawasaki disease (KD) is a systemic vasculitis of unknown etiology, predominantly affecting coronary arteries. It has emerged as the most common acquired heart disease in children in developed countries [1]. Without timely intervention, up to 25% of pediatric patients may develop coronary artery dilatation or coronary artery aneurysms (CAAs), which can lead to myocardial ischemia, myocardial

infarction, and potentially fatal outcomes [2]. Furthermore, 10%–20% of KD patients exhibit resistance to first-line therapy with intravenous immunoglobulin (IVIG) and aspirin. While this primary treatment regimen has decreased the incidence of coronary artery lesions (CALs) to approximately 5%, patients with refractory KD remain at a heightened risk of developing CAAs. In recent years, there has been an observed increase in both IVIG resistance rates and the incidence of CALs [3,4]. The advent of biological agents offers a promising alternative for treating refractory KD, demonstrating significant clinical efficacy. In this review, we summarize the pathogenesis of KD and discuss the targeted anti-inflammatory effects and clinical advancements of biologic agents in the treatment of KD based on its pathogenesis; we also briefly discuss the types, mechanisms of action, dosage, administration, and adverse effects of biologics used in the treatment of KD.

2. Pathogenesis of KD

The pathogenesis of KD has not been fully elucidated. Current research suggests that its etiology is associated with genetic predisposition, vaccine exposure theory, infections, environmental and seasonal factors, and immune imbalance.

(1) Genetic predisposition: KD exhibits a higher prevalence in Asian populations, particularly among Japanese individuals. Additionally, the incidence of KD is significantly elevated in children whose siblings or parents have been diagnosed with KD [5,6]. Genes linked to KD can be categorized into four groups: (i) enhanced T-cell activation (e.g., *ITPKC*, *ORAI1*, *STIM1*), in which single nucleotide polymorphisms (SNP) in ITPKC may lead to an increase in IL-1β by activating of NLRP3 and contribute to an increase in the release of interleukin-2 (IL-2) by enhancing T-cell activation. Abnormally elevated levels of the above cytokines lead to damage to vascular endothelial cells, which will aggravate the clinical manifestations of KD and increase the risk of CALs. In Japan, SNP in ITPKC is associated with the risk of CALs, while the same ITPKC in China is related to susceptibility of KD. (ii) B-cell signaling disorders (e.g., *CD40*, *BLK*, *FCGR2A*), in which the FCGR2A encodes the human FCGR (a key protein linking the adaptive and innate immune systems), and upregulation of this family of receptors during the acute phase of KD increases monocyte and neutrophil activation, thereby exacerbating the inflammatory response. (iii) Cellular apoptosis (e.g., *CASP3*), in addition to its apoptosis-inducing effects; CASP3 interacts with T-cell receptors, resulting in an increase in CASP3 transcription and activation of the nuclear factor signaling pathway in activated T cells, which ultimately leads to elevated cytokine levels. (iv) Alterations in transforming growth factor β (TGF-β) signaling (e.g., *TGFB2*, *TGFBR2*, *MMP*, *SMAD*); the SNP in genes associated with the TGF-β pathway downregulates the Treg immune response, which is positively correlated with the risk of developing KD and the incidence of CAAs. In addition, activated TGF-β is associated with T-cell activation and cardiovascular remodeling, both of which contribute to the progression of KD [5–8].

(2) Vaccine exposure theory: Several studies have investigated the potential role of vaccinations in inducing KD through robust stimulation of both innate and adaptive immune responses. However, no definitive evidence has been found linking vaccination to the onset of KD [9].

(3) Infection: Research has demonstrated that the development of KD is associated with a wide range of pathogenic infections. These include DNA viruses such as Epstein–Barr virus, human adenovirus, and human parvovirus B19, as well as RNA viruses including Coxsackievirus, enterovirus, influenza virus, and severe acute respiratory syndrome coronavirus-2. Additionally, bacterial pathogens such as *Staphylococcus aureus* and group A *Streptococcus* have been implicated.

Furthermore, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Rickettsia* can also contribute to KD onset [10].

(4) Environment and seasonality: The incidence of KD appears to be influenced by seasonal variations in different countries. For instance, higher KD incidence rates during winter and spring in non-temperate climates suggest a correlation with specific viral infections [11].

(5) Immune response: The innate immune system can be activated by detecting pathogen-associated molecular patterns or damage-associated molecular patterns. Early activation of the innate immune system is characterized by the mobilization of circulating neutrophils and the production of pro-inflammatory cytokines such as IL-1, IL-6, and tumor necrosis factor (TNF). The NLRP3 inflammatory vesicle is a key component of the innate immune system that recognizes these aberrant molecular patterns in vivo and mediates caspase-1 activation and pro-inflammatory cytokine secretion during microbial infection and cellular injury. Moreover, studies on adaptive immunity indicate that both pro-inflammatory and regulatory T cells are detectable in the circulation within the first week following fever onset [12,13]. Inflammatory cytokines such as IL-1 and TNF-α also promote the aggregation and activation of inflammatory cells and the release of inflammatory mediators. Matrix metalloproteinase (MMP) is involved in extracellular remodeling in KD and is associated with the development of CALs in patients with KD; IL-1β, IL-6, and TNF-α stimulate the expression of MMP-9, leading to tissue damage and stress, which in turn triggers inflammatory responses and CAAs formation [14].

3. Diagnostic criteria and treatment of KD

The diagnostic criteria and primary treatment protocols for KD were established according to the 2024 American Heart Association Scientific Statement on the Diagnosis and Management of KD [15].

4. Treatment of KD with biologic agents

As research on KD has advanced, it has become evident that biological agents are effective for children who do not respond adequately to first-line treatments. Currently, biologic agents are employed in the clinical management of KD. These include anti-TNF-alpha (TNF-α) antagonists, IL-1 receptor antagonists, anti-CD20 monoclonal antibodies, IL-6 receptor antagonists, and platelet glycoprotein IIb/IIIa receptor inhibitors.

4.1. Anti-TNF-α antagonists

TNF-α is a pro-inflammatory cytokine that plays a crucial role in the host's defense against infection and in modulating immune responses. While physiologically produced TNF-α exerts protective effects, its overproduction can be detrimental or even lethal to the organism. Excessive TNF-α levels are linked to chronic inflammation observed in immunomodulatory inflammatory diseases. Early in vitro studies have demonstrated that TNF-α present in the serum of children with KD induces endothelial cell apoptosis. Moreover, the significant elevation of TNF-α in the serum of children with acute-phase KD directly induces vascular endothelial cells to express intercellular adhesion molecule-1 (ICAM-1) and monocyte chemotactic protein-1 (MCR-1), which promotes the infiltration of inflammatory cells, thereby exacerbating vascular injury and inducing CALs [16–18]. Consequently,

controlling TNF-α levels or inhibiting its receptor binding is essential for mitigating inflammation in KD patients. TNF-α antagonists can be categorized into two main types: monoclonal antibodies and soluble receptors. Infliximab (IFX), a chimeric monoclonal antibody targeting TNF-α, and Etanercept, a soluble TNF receptor fusion protein, represent key examples of these therapeutic agents [19].

4.4.1. IFX

IFX was first utilized in the treatment of children with refractory KD in 2004 and has since become an accepted therapeutic option for patients unresponsive to IVIG therapy [20]. IFX is a human-mouse chimeric monoclonal antibody that exerts its anti-inflammatory effects through multiple mechanisms, including (1) neutralization of soluble TNF-α, (2) dissociation of TNF-α from its receptor, and (3) elimination of TNF-α-producing macrophages and activated T cells via antibody-dependent or complement-dependent cytotoxicity. Specifically, IFX blocks TNF-α by binding to it and preventing its interaction with its receptor, thereby inhibiting neutrophil activation. Additionally, IFX can eliminate activated T cells and CD14 and CD16 monocytes and inhibit the release of inflammatory cytokines such as TNF-α, IL-1, IL-2, and IL-6 through cytotoxic effects. Furthermore, depending on the local cytokine environment, IFX can induce the differentiation of naive CD4 Th cells into Th17 and regulatory T-cell (Treg) phenotypes [18,21]. Moreover, IFX inhibits major inflammatory cytokine pathways, including TNF-α, IL-1, IL-2, and IL-6, and suppresses these pathways at the transcriptional levels of peptidase inhibitor-3, matrix metalloproteinase-8, chemokine receptor-2, and pentraxin-3. It further inhibits elastase secretion from neutrophils and reduces their adhesion to vascular endothelial cells during the acute phase, thereby mitigating arterial vascular endothelial inflammation. However, while IFX effectively suppresses systemic inflammation in KD patients, it does not completely prevent local vasculitis [18,22].

IFX infusion in children with KD can effectively alleviate fever, mitigate inflammation, improve arthritic symptoms, reduce the frequency of plasma exchanges, lower hospitalization rates, and prevent the progression of CALs [18,20,23]. Compared to traditional IVIG therapy, the combination of IFX and IVIG can decrease the incidence of drug resistance and shorten the clinical course for KD patients who are resistant to IVIG, without a significant increase in adverse events [24]. According to the newly revised guidelines, IFX is classified as third-line therapy; however, for patients who do not respond well to first-line treatments, IFX can be escalated to second-line therapy [22]. Adverse effects associated with IFX administration include rash, arthritis, respiratory issues, infusion reactions, hepatomegaly, and vaccine-related complications, but these occur at a very low frequency [18].

4.1.2. Etanercept

Etanercept is a soluble TNF receptor fusion protein classified among the TNF-α antagonists. It specifically binds to TNF-α, thereby inhibiting inflammatory responses by blocking the interaction between TNF-α and its cell surface receptor [25,26]. Previous studies have demonstrated that etanercept treatment in KD not only reduces TNF-α levels but also decreases levels of IL-6, IL-12, IL-13, and IL-17. Consequently, some experts hypothesize that etanercept may reduce other cytokine levels by inhibiting the effects of TNF-α or lymphotoxin, thus mitigating vascular inflammation [26]. Although using etanercept as primary adjuvant therapy in acute KD does not alter the final outcome of CALs, it may facilitate early relief of arterial dilatation. Importantly, several studies have shown that combining etanercept with IVIG therapy can shorten disease duration and reduce sequelae in

atypical KD patients, while enhancing IVIG sensitivity when administered within the first 10 days of the disease [25,27]. Regarding safety, etanercept, being fully humanized, carries a lower risk of drug-targeting autoantibodies and transfusion reactions compared to IFX, and it clears more rapidly [27]. Currently, etanercept has been utilized in infants with refractory KD, with clinical observations indicating significant improvements in inflammation and fever resolution [28]. However, further verification of its efficacy and safety through larger clinical studies is necessary.

4.2. IL-1 receptor antagonists

IL-1 mediates both local and systemic inflammatory responses and plays a pivotal role in the pathogenesis of rheumatic and autoinflammatory diseases. In the IL-1 family, IL-1α and IL-1β are typical pro-inflammatory cytokines, both of which bind and activate the same IL-1 receptor. IL-1β is transcribed as an inactive precursor, which requires the assembly of NLRP3 inflammasome vesicles to activate Caspase 1, which in turn mediates inflammation and enhances antigen-driven $CD8^+$ T-cell differentiation, proliferation, memory, and migration to the tissues. On the other hand, IL-1α, upon release from necrotic cells at the site of injury, can directly bind to IL-1 receptors on neighboring cells and activate a cascade of inflammatory cytokines and chemokines. In a KD mouse model, IL-1α and IL-1β were shown to play key roles in LCWE-induced KD vasculitis and myocarditis, and IL-1α was not only associated with inflammatory thrombosis but was also involved in CALs formation [29–31]. In KD patients, IL-1 promotes antigen-driven differentiation, proliferation, and tissue migration of $CD8^+$ T cells. It may also infiltrate the coronary artery wall, inducing the proliferation of smooth muscle cells and myofibroblasts, prolonging neutrophil survival, and stimulating matrix metalloproteinases, thereby contributing to the development and progression of CAAs [32].

4.2.1. Anakinra (ANA)

ANA is a recombinant IL-1 receptor antagonist that specifically blocks IL-1α and IL-1β by antagonizing the IL-1 receptor. This action prevents the cascade of sterile inflammation and inflammasome assembly in pathological conditions [33,34]. Although monoclonal antibodies that blocked specific functions of IL-1α or IL-1β alone significantly reduced the development of KD vasculitis, simultaneous blockade of both cytokines was more effective in preventing the formation of any KD lesions [29]. ANA not only facilitates complete recovery from aneurysms but also promotes true remodeling of coronary arteries. Importantly, it exhibits an excellent safety profile in pediatric patients, characterized by rapid onset of action, a short half-life, and dual blockade of both IL-1α and IL-1β [34,35]. Clinical studies have demonstrated that ANA effectively controls KD, significantly reduces fever and inflammatory responses, and improves coronary artery dilation in over 90% of KD patients [36]. In the use of ANA in the treatment of KD, most studies have used 2–10 mg/kg/d; the most common adverse effects were fever and injection site rash, which resolved rapidly, and no associated serious adverse effects have been identified. Both intravenous injection (IV) and subcutaneous injection (SC) ANA have a favorable safety profile and are well tolerated in children with KD; more frequent IV administration may result in more sustained concentrations compared with SC administration, while multiple SC injections can be avoided without significantly increasing peak concentrations. The use of high-dose ANA has been reported to be effective in the treatment of KD combined with macrophage activation syndrome [37–43].

It can be seen that the dose of ANA in KD treatment needs to be selected according to the different conditions of the child.

4.2.2. Canakinumab

Canakinumab is a recombinant human monoclonal antibody that specifically targets IL-1β by inhibiting its interaction with the IL-1 receptor, hence preventing the activation of inflammatory responses [35,44]. In a 2017 European Phase II multicenter trial evaluating canakinumab in KD patients, participants were categorized into two groups: an untreated complete KD group and an IVIG-resistant KD group. The first group received an initial intravenous dose of 6 mg/kg canakinumab, followed by one or two subsequent subcutaneous injections at weeks 4 and 8, contingent upon C-reactive protein levels and clinical follow-up. The second group received the same initial intravenous dose, with repeat administrations at weeks 4 and 8 post-initial treatment. Clinical studies have demonstrated that canakinumab exhibits favorable efficacy and safety profiles, with no adverse reactions reported [42].

4.3. Anti-CD20 monoclonal antibody: Rituximab

Rituximab was first introduced in 1980 for the treatment of B-cell lymphomas. This chimeric mouse-human monoclonal antibody targets the CD20 surface antigen specifically expressed on B cells. CD20, a glycosylated transmembrane protein, is predominantly found on the surface of both malignant and normal B cells. Its stable expression on the cell surface, without shedding or internalization upon antibody binding, makes it an ideal target for therapeutic intervention [45–48]. Rituximab binds to antigens exclusively present on mature B cells and exerts its effects through three primary mechanisms: Complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and direct induction of apoptosis in target cells. These mechanisms lead to the depletion of B-cell activity, thereby playing a significant role in the treatment of autoimmune diseases [46].

In 2012, Sauvaget et al. reported a case of KD that exhibited resistance to IVIG and systemic corticosteroids, resulting in severe CALs due to uncontrolled progression of the disease. However, following treatment with rituximab at a dose of 15 mg/kg/day, both the clinical symptoms and overall condition of the patient were effectively managed. Notably, the CALs and coronary artery dimensions gradually normalized [47].

4.4. IL-6 receptor antagonist: Tocilizumab (TCZ)

IL-6 is a pleiotropic cytokine primarily produced by neutrophils and monocytes/macrophages. It has been shown to downregulate $FOXP3^+$ Tregs, promote the conversion of pro-inflammatory Tregs, and diminish Treg stability, thereby exacerbating acute vasculitis. Additionally, IL-6 can induce thrombocytosis and contribute to vasculitis and endothelial injury through the initiation of a cascade of inflammatory reactions. Studies have demonstrated that IL-6 levels are significantly elevated in IVIG-resistant KD patients compared to those who are IVIG-sensitive [49,50].

TCZ is an IL-6 receptor antagonist and a humanized monoclonal antibody that inhibits IL-6 signaling by blocking both membrane-bound and soluble forms of the IL-6 receptor, thereby exerting targeted anti-inflammatory effects. It has been extensively utilized in the treatment of autoimmune

diseases. Given the bidirectional regulatory nature of IL-6, this cytokine can bind to its receptor to activate the gp130 pathway under stress conditions, aiding in the elimination of pathogens and promoting tissue repair. However, during infection or tissue injury, excessive IL-6 expression can induce pro-inflammatory responses [51,52]. Therefore, the timing of medication administration is crucial. During the coronavirus disease 2019 pandemic, accumulating evidence suggested that TCZ can mitigate cytokine storms associated with multisystem inflammatory syndrome in children, which shares clinical features with KD [53]. A small retrospective study conducted in 2024 demonstrated that in KD patients resistant to IVIG, the administration of TCZ led to gradual resolution of KD-related symptoms and effective control of systemic inflammation [50], with no adverse reactions observed. Conversely, a prospective study from 2017 indicated that TCZ treatment in KD patients might be associated with CAAs [54]. Due to the limited number of studies and small sample sizes, further research is necessary to fully evaluate the efficacy and safety of TCZ in KD treatment.

In our opinion, the treatment of KD using biologics belongs to targeted therapy, because TCZ belongs to IL-6 receptor antagonists, which may be ineffective in treating KD that is not dominated by IL-6 elevation, which may be the reason for the contradictory therapeutic effects. Therefore, we should dynamically monitor the cytokine levels of the children before and after the use of TCZ for KD treatment to choose the appropriate biologics.

4.5. Platelet glycoprotein IIb/IIIA receptor inhibitor: Abciximab

Coronary artery thrombosis represents the primary cause of mortality in children with KD. Despite initial treatment, 5% of KD pediatric patients still exhibit transient coronary artery dilation, while 1% develop CAAs. Notably, these giant CAAs are susceptible to stasis, which can result in thrombosis and stenosis at both the proximal and distal ends of the CAAs, potentially leading to myocardial infarction [55,56].

Abciximab is a potent inhibitor of the platelet glycoprotein IIb/IIIa receptor, which is situated on the platelet membrane and mediates platelet aggregation. Consequently, abciximab effectively blocks platelet aggregation by directly inhibiting these receptors. In addition to preventing platelet adhesion to endothelial cells, abciximab also inhibits platelet adhesion to leukocytes and mitigates the inflammatory process through its action on the αmβ2 integrin receptor [55]. Research has demonstrated that while abciximab does not induce regression of coronary aneurysms, it successfully prevents thrombotic complications and promotes vascular remodeling [56,57]. A case report on KD with CAAs suggests that the combination of tissue plasminogen activator and abciximab may be crucial in treating myocardial infarction caused by coronary artery thrombosis in KD patients with CAAs [56]. Based on the current study, it has been shown that abciximab is prognostically beneficial in KD with severe CALs, and that regression of the CALs is more pronounced when treated with abciximab on top of first-line therapy compared with first-line therapy only [55]. Abciximab has been utilized for treating acute coronary syndrome in adults. Still, there are significant physiologic differences between adults and children, and studies on abciximab in the treatment of KD are limited to small-sample studies; its optimal dosage for the treatment of KD, duration of treatment, long-term effects, and complications need to be further substantiated by a larger number of studies.

The dosage and adverse reactions of commonly used biologic agents are presented in Table 1. The pathogenesis of KD and the therapeutic mechanism of biologics are presented in Figure 1.

Table 1. Dosage and adverse reactions of commonly used biologic agents.

Classification	Drug	Dosage and usage	Adverse reaction	References
TNF-α antagonists	Inflixmab	10 mg/kg, IV, over 2 hours		[15]
		5 mg/kg, IV	Cutaneous eruptions, arthritic conditions, respiratory disorders, infusion-related reactions, hepatomegaly, and complications associated with vaccination	[18]
	Etanercept	0.8 mg/kg, SC, three times per week		[15]
IL-1 receptor antagonist	Anakinra	10 mg/kg/d, IV/SC		[15]
		6 mg/kg/d, SC, discontinued directly after 9 weeks		[40]
		2 mg/kg/d, SC, 2 weeks		[41]
		2–6 mg/kg/d, SC, 2 weeks		[42]
		2 mg/kg, IV, gradually increased to a maximum of 10 mg/kg	Liver damage	[43]
	Canakinumab	6 mg/kg, IV, repeated at weeks 4 and 8		[42]
Anti-CD20 monoclonal antibody	Rituximab	15 mg/kg/d, IV drop		[47]
IL-6 receptor antagonist	Tocilizumab	12 mg/kg/d (<30kg), IV drop		[50]
		8 mg/kg/d (>30kg), IV drop		
Platelet glycoprotein IIb/IIIa receptor inhibitor	Abciximab	0.25 mg/kg, IV, followed by a 12-h IV drop of 0.125 μg/kg/min. Median day was 17 (range: 9–40)		[57]

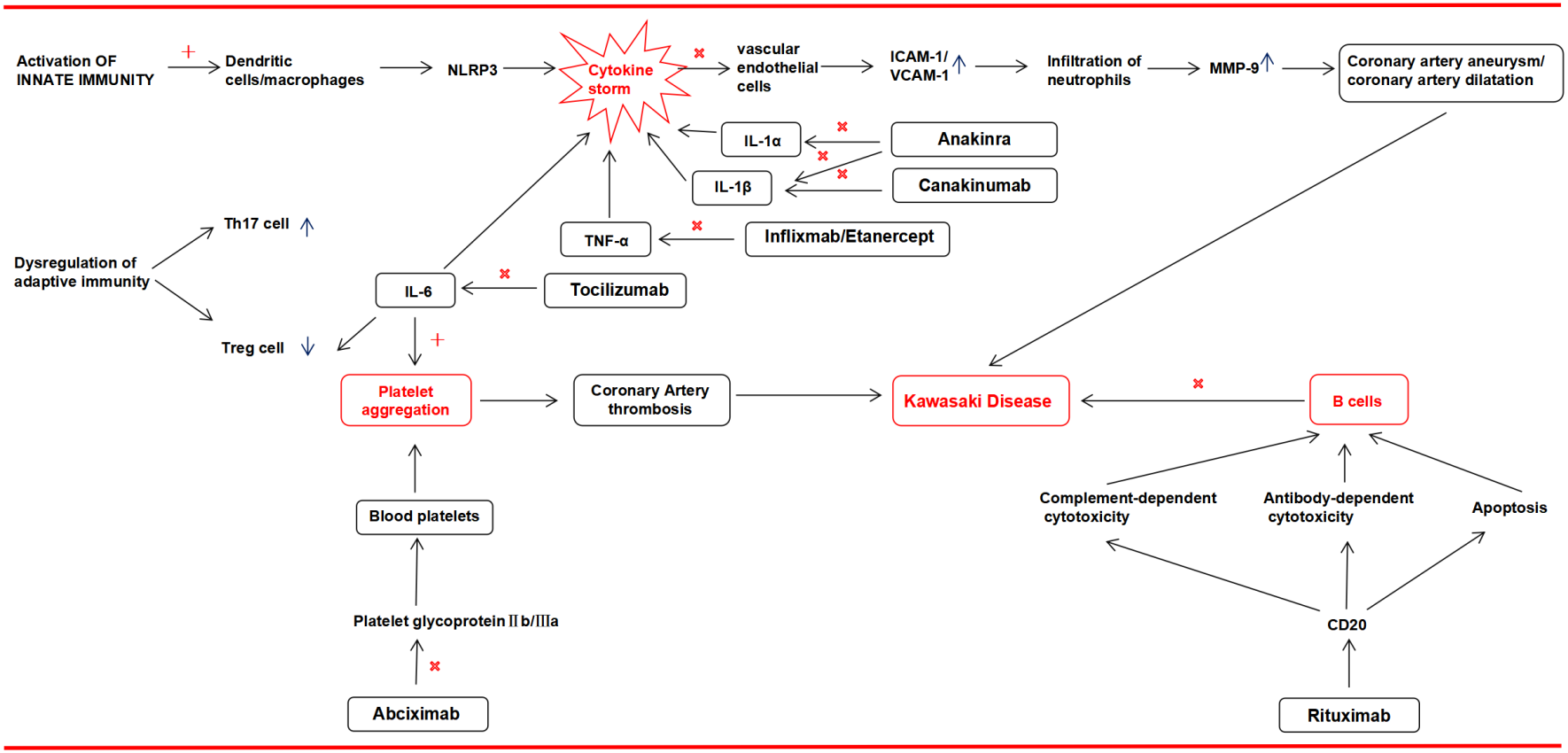

Figure 1. Pathogenesis of KD and the therapeutic mechanism of biologics.

5. Conclusion

It is widely recognized that not all patients with KD respond adequately to first-line therapy, and a subset of KD patients may develop refractory KD, thereby increasing the risk of CALs. The advent of biological agents offers a promising alternative for managing refractory KD. Currently, biological agents used for the treatment of KD are mainly divided into five categories: anti-TNF-α antagonists, IL-1 receptor antagonists, anti-CD20 monoclonal antibodies, IL-6 receptor antagonists, and platelet glycoprotein IIb/IIIa receptor inhibitors. Among the anti-TNF-α antagonists, IFX and Etanercept have been used in the treatment of KD, both of which can inhibit the interaction of TNF-α with the receptor by competitively binding to TNF-α, which not only reduces the level of TNF-α but also downregulates the expression of related pro-inflammatory factors, thus exerting anti-inflammatory effects. Notably, IFX prevents the progression of CALs, and Etanercept promotes early remission of arterial dilatation and enhances IVIG sensitivity. Although the overall safety profile of both drugs is favorable, contraindications in special populations should be noted: IFX should be used with caution in KD with comorbidities such as skin rashes or abnormalities in hepatic function. Among IL-1 receptor antagonists, ANA and Canakinumab have been shown to be useful in the treatment of KD, both of which work by blocking the IL-1 signaling pathway. ANA antagonizes the effects of both IL-1α and IL-1β, whereas Canakinumab selectively inhibits IL-1β and IL-1 receptor binding. Available clinical data suggest that treatment with ANA may cause liver function abnormalities, whereas no adverse effects have been reported with Canakinumab. Therefore, for KD patients with combined hepatic function abnormalities, it is recommended to prioritize Canakinumab or other alternative treatments. The other three types of biologics need to be selected according to the different characteristics of patients because of their different mechanisms of action. It is recommended to dynamically monitor the changes in serum cytokine profiles before and after treatment with biologics in the clinic, so as to reduce the risk of adverse reactions through biomarker-guided precision dosing.

However, it is crucial to exclude infection-related factors prior to initiating biological agent therapy. Additionally, at the level of treatment selection, it is necessary to comprehensively assess the child's condition, drug indications, and potential adverse effects, and to implement individualized treatment plans and dynamically monitor serum cytokine levels based on a precise assessment of the efficacy and safety profiles of biologics with different target sites. Currently, the pathogenesis of KD has not been fully elucidated, and the clinical application of biologics in this field still has many limitations, mainly focusing on the intervention of classical inflammatory pathways such as TNF-α and IL-1. With the breakthrough progress of molecular immunology and genomics research, more key signaling pathways and potential therapeutic targets may be revealed in the future, which will provide a theoretical basis and innovative direction for the development of new biological agents.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Conflict of interest

All authors declare that they have no conflict of interest in relation to this paper.

Author contributions

Zhang WH and Yin QL contributed to conception and design of the study; Yin QL wrote the first draft of the manuscript; all authors contributed to editing of the manuscript.

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References

1. Miyata K, Miura M, Kaneko T, et al. (2021) Risk factors of coronary artery abnormalities and resistance to intravenous immunoglobulin plus corticosteroid therapy in severe Kawasaki disease: An analysis of post RAISE. *Circ Cardiovasc Qual Outcomes* 14: e007191. https://doi.org/10.1161/CIRCOUTCOMES.120.007191
2. Lei WT, Chang LS, Zeng BY, et al. (2022) Pharmacologic interventions for Kawasaki disease in children: A network meta-analysis of 56 randomized controlled trials. *EBioMedicine* 78: 103946. https://doi.org/10.1016/j.ebiom.2022.103946
3. Kibata T, Suzuki Y, Hasegawa S, et al. (2016) Coronary artery lesions and the increasing incidence of Kawasaki disease resistant to initial immunoglobulin. *Int J Cardiol* 214: 209–215. https://doi.org/10.1016/j.ijcard.2016.03.017
4. Ohnishi Y, Okada S, Kawakami-Miyake A, et al. (2022) Safety and feasibility of infliximab therapy in children with Kawasaki disease who received live vaccinations. *Pediatr Infect Dis J* 41: e388–e392. https://doi.org/10.1097/INF.0000000000003611
5. Tang B, Lo HH, Lei C, et al. (2020) Adjuvant herbal therapy for targeting susceptibility genes to Kawasaki disease: An overview of epidemiology, pathogenesis, diagnosis and pharmacological treatment of Kawasaki disease. *Phytomedicine* 70: 153208. https://doi.org/10.1016/j.phymed.2020.153208
6. Chang L, Yang HW, Lin TY, et al. (2021) Perspective of immunopathogenesis and immunotherapies for Kawasaki disease. *Front Pediatr* 9: 697632. https://doi.org/10.3389/fped.2021.697632
7. Kumrah R, Vignesh P, Rawat A, et al. (2020) Immunogenetics of Kawasaki disease. *Clin Rev Allergy Immunol* 59: 122–139. https://doi.org/10.1007/s12016-020-08783-9
8. Paolini L, Guida F, Calvaruso A, et al. (2024) Endothelial dysfunction: Molecular mechanisms and therapeutic strategies in Kawasaki disease. *Int J Mol Sci* 25: 13322. https://doi.org/10.3390/ijms252413322
9. Rife E, Gedalia A (2020) Kawasaki disease: An update. *Curr Rheumatol Rep* 22: 75. https://doi.org/10.1007/s11926-020-00941-4

10. Wang W, Zhu L, Li X, et al. (2023) Emerging evidence of microbial infection in causing systematic immune vasculitis in Kawasaki disease. *Front Microbiol* 14: 1313838. https://doi.org/10.3389/fmicb.2023.1313838
11. Chang LY, Lu CY, Shao PL, et al. (2014) Viral infections associated with Kawasaki disease. *J Formos Med Assoc* 113: 148–154. https://doi.org/10.1016/j.jfma.2013.12.008
12. McCrindle BW, Rowley AH, Newburger JW, et al. (2017) Diagnosis, treatment, and long-term management of Kawasaki disease: A scientific statement for health professionals from the American Heart Association. *Circulation* 135: e927–e999. https://doi.org/10.1161/CIR.0000000000000484
13. Bordea MA, Costache C, Grama A, et al. (2022) Cytokine cascade in Kawasaki disease versus Kawasaki-like syndrome. *Physiol Res* 71: 17–27. https://doi.org/10.33549/physiolres.934672
14. Zhang H, Song HB, Wang DX, et al. (2022) Correlation between the level of inflammatory cytokines and prognosis in children with IVIG-sensitive Kawasaki disease and IVIG-resistant Kawasaki disease. *Pak J Med Sci* 38: 1165–1169. https://doi.org/10.12669/pjms.38.5.5408
15. Jone PN, Tremoulet A, Choueiter N, et al. (2024) Update on diagnosis and management of Kawasaki disease: A scientific statement from the American Heart Association. *Circulation* 150: e481–e500. https://doi.org/10.1161/CIR.0000000000001295
16. Yamaji N, da Silva Lopes K, Shoda T, et al. (2019) TNF-α blockers for the treatment of Kawasaki disease in children. *Cochrane Database Syst Rev* 8: CD012448. https://doi.org/10.1002/14651858.CD012448.pub2
17. Li D, Li X, Dou W, et al. (2021) The effectiveness of infliximab for Kawasaki disease in children: Systematic review and meta-analysis. *Transl Pediatr* 10: 1294–1306. https://doi.org/10.21037/tp-20-482
18. Chen J, Liao J, Xiang L, et al. (2023) Current knowledge of TNF-α monoclonal antibody infliximab in treating Kawasaki disease: A comprehensive review. *Front Immunol* 14: 1237670. https://doi.org/10.3389/fimmu.2023.1237670
19. Portman MA, Olson A, Soriano B, et al. (2011) Etanercept as adjunctive treatment for acute Kawasaki disease: Study design and rationale. *Am Heart J* 161: 494–499. https://doi.org/10.1016/j.ahj.2010.12.003
20. Kabbaha S, Milano A, Aldeyab MA, et al. (2023) Infliximab as a second-line therapy for children with refractory Kawasaki disease: A systematic review and meta-analysis of randomized controlled trials. *Br J Clin Pharmacol* 89: 49–60. https://doi.org/10.1111/bcp.15547
21. Koizumi K, Hoshiai M, Katsumata N, et al. (2018) Infliximab regulates monocytes and regulatory T cells in Kawasaki disease. *Pediatr Int* 60: 796–802. https://doi.org/10.1111/ped.13555
22. Ishii M, Ebato T, Kato H (2020) History and future of treatment for acute stage Kawasaki disease. *Korean Circ J* 50: 112–119. https://doi.org/10.4070/kcj.2019.0290
23. Hur G, Song MS, Sohn S, et al. (2019) Infliximab treatment for intravenous immunoglobulin-resistant Kawasaki disease: A multicenter study in Korea. *Korean Circ J* 49: 183–191. https://doi.org/10.4070/kcj.2018.0214
24. Li X, Tang Y, Ding Y, et al. (2021) Higher efficacy of infliximab than immunoglobulin on Kawasaki disease, a meta-analysis. *Eur J Pharmacol* 899: 173985. https://doi.org/10.1016/j.ejphar.2021.173985
25. Portman MA, Dahdah NS, Slee A, et al. (2019) Etanercept with IVIG for acute Kawasaki disease: A randomized controlled trial. *Pediatrics* 143: e20183675. https://doi.org/10.1542/peds.2018-3675

26. Ohashi R, Fukazawa R, Watanabe M, et al. (2013) Etanercept suppresses arteritis in a murine model of kawasaki disease: A comparative study involving different biological agents. *Int J Vasc Med* 2013: 543141. https://doi.org/10.1155/2013/543141
27. Sagiv E, Slee A, Buffone A, et al. (2023) Etanercept with IVIG for acute Kawasaki disease: A long-term follow-up on the EATAK trial. *Cardiol Young* 33: 613–618. https://doi.org/10.1017/S1047951122001470
28. Tremoulet AH (2018) Adjunctive therapies in Kawasaki disease. *Int J Rheum Dis* 21: 76–79. https://doi.org/10.1111/1756-185X.13208
29. Lee Y, Wakita D, Dagvadorj J, et al. (2015) IL-1 signaling is critically required in stromal cells in Kawasaki disease vasculitis mouse model: Role of both IL-1α and IL-1β. *Arterioscler Thromb Vasc Biol* 35: 2605–2616. https://doi.org/10.1161/ATVBAHA.115.306475
30. Cavalli G, Colafrancesco S, Emmi G, et al. (2021) Interleukin 1α: A comprehensive review on the role of IL-1α in the pathogenesis and treatment of autoimmune and inflammatory diseases. *Autoimmun Rev* 20: 102763. https://doi.org/10.1016/j.autrev.2021.102763
31. Maniscalco V, Abu-Rumeileh S, Mastrolia MV, et al. (2020) The off-label use of anakinra in pediatric systemic autoinflammatory diseases. *Ther Adv Musculoskelet Dis* 12: 1759720X20959575. https://doi.org/10.1177/1759720X20959575
32. Mastrolia MV, Abbati G, Signorino C, et al. (2021) Early anti IL-1 treatment replaces steroids in refractory Kawasaki disease: Clinical experience from two case reports. *Ther Adv Musculoskelet Dis* 13: 1759720X211002593. https://doi.org/10.1177/1759720X211002593
33. De Rose DU, Campi F, Maddaloni C, et al. (2025) Off-label use of anakinra in inflammatory conditions in neonates and infants up to 3 months of age: A case series and a review of the literature. *Paediatr Drugs* 27: 293–305. https://doi.org/10.1007/s40272-024-00679-x
34. Bossi G, Codazzi AC, Vinci F, et al. (2022) Efficacy of anakinra on multiple coronary arteries aneurysms in an infant with recurrent Kawasaki disease, complicated by macrophage activation syndrome. *Children* 9: 672. https://doi.org/10.3390/children9050672
35. Ferrara G, Giani T, Caparello MC, et al. (2020) Anakinra for treatment-resistant Kawasaki disease: Evidence from a literature review. *Paediatr Drugs* 22: 645–652. https://doi.org/10.1007/s40272-020-00421-3
36. Malcova H, Milota T, Strizova Z, et al. (2021) Interleukin-1 blockade in polygenic autoinflammatory disorders: Where are we now? *Front Pharmacol* 11: 619273. https://doi.org/10.3389/fphar.2020.619273
37. Yang J, Jain S, Capparelli EV, et al. (2021) Anakinra treatment in patients with acute Kawasaki disease with coronary artery aneurysms: A phase I/IIa trial. *J Pediatr* 243: 173–180.e8. https://doi.org/10.1016/j.jpeds.2021.12.035
38. Lind-Holst M, Hartling UB, Christensen AE (2019) High-dose anakinra as treatment for macrophage activation syndrome caused by refractory Kawasaki disease in an infant. *BMJ Case Rep* 12: e229708. https://doi.org/10.1136/bcr-2019-229708
39. Shafferman A, Birmingham JD, Cron RQ (2014) High dose anakinra for treatment of severe neonatal Kawasaki disease: A case report. *Pediatr Rheumatol Online J* 12: 26. https://doi.org/10.1186/1546-0096-12-26
40. Gambacorta A, Buonsenso D, De Rosa G, et al. (2020) Resolution of giant coronary aneurisms in a child with refractory Kawasaki disease treated with anakinra. *Front Pediatr* 8: 195. https://doi.org/10.3389/fped.2020.00195

41. Sánchez-Manubens J, Gelman A, Franch N, et al. (2017) A child with resistant Kawasaki disease successfully treated with anakinra: A case report. *BMC Pediatr* 17: 102. https://doi.org/10.1186/s12887-017-0852-6
42. Burns JC, Koné-Paut I, Kuijpers T, et al. (2017) Review: Found in translation: International initiatives pursuing interleukin-1 blockade for treatment of acute Kawasaki disease. *Arthritis Rheumatol* 69: 268–276. https://doi.org/10.1002/art.39975
43. Martins FR, Azevedo AC, Ganhão S, et al. (2023) Anakinra and hepatotoxicity in pediatric rheumatology: A case series. *Pediatr Rheumatol Online J* 21: 112. https://doi.org/10.1186/s12969-023-00891-y
44. Malcova H, Strizova Z, Milota T, et al. (2021) IL-1 Inhibitors in the treatment of monogenic periodic fever syndromes: From the past to the future perspectives. *Front Immunol* 11: 619257. https://doi.org/10.3389/fimmu.2020.619257
45. Renner C (2019) 20 years of rituximab treatment: What have we learnt? *Future Oncol* 15: 4119–4121. https://doi.org/10.2217/fon-2019-0694
46. Lucchini E, Zaja F, Bussel J (2019) Rituximab in the treatment of immune thrombocytopenia: What is the role of this agent in 2019? *Haematologica* 104: 1124–1135. https://doi.org/10.3324/haematol.2019.218883
47. Sauvaget E, Bonello B, David M, et al. (2012) Resistant Kawasaki disease treated with anti-CD20. *J Pediatr* 160: 875–876. https://doi.org/10.1016/j.jpeds.2012.01.018
48. Tacke CE, Burgner D, Kuipers IM, et al. (2012) Management of acute and refractory Kawasaki disease. *Expert Rev Anti Infect Ther* 10: 1203–1215. https://doi.org/10.1586/eri.12.101
49. Wu Y, Liu FF, Xu Y, et al. (2019) Interleukin-6 is prone to be a candidate biomarker for predicting incomplete and IVIG nonresponsive Kawasaki disease rather than coronary artery aneurysm. *Clin Exp Med* 19: 173–181. https://doi.org/10.1007/s10238-018-00544-5
50. Ling J, Xie F, Zhou Q, et al. (2024) Case series on the efficacy and safety of tocilizumab in IVIG-resistant Kawasaki disease: A retrospective analysis of five patients. *J Inflamm Res* 17: 10991–10998. https://doi.org/10.2147/JIR.S479879
51. Cui HY, Hu CP (2022) Recent research on the application of biologics in the treatment of multisystem inflammatory syndrome in children after SARS-CoV-2 infection. *Zhongguo Dang Dai Er Ke Za Zhi* 24: 216–222. https://doi.org/10.7499/j.issn.1008-8830.2111005
52. Porritt RA, Chase Huizar C, Dick EJ, et al. (2021) Inhibition of IL-6 in the LCWE mouse model of Kawasaki disease Inhibits acute phase reactant serum amyloid a but fails to attenuate vasculitis. *Front Immunol* 12: 630196. https://doi.org/10.3389/fimmu.2021.630196
53. Barman P, Pilania RK, Cv G, et al. (2024) Treatment intensification in Kawasaki disease-current perspectives. *Expert Rev Clin Immunol* 20: 1179–1191. https://doi.org/10.1080/1744666X.2024.2378900
54. Nozawa T, Imagawa T, Ito S (2017) Coronary-artery aneurysm in tocilizumab-treated Children with Kawasaki's Disease. *N Engl J Med* 377: 1894–1896. https://doi.org/10.1056/NEJMc1709609
55. Bachlava E, Loukopoulou S, Karanasios E, et al. (2016) Management of coronary artery aneurysms using abciximab in children with Kawasaki disease. *Int J Cardiol* 220: 65–69. https://doi.org/10.1016/j.ijcard.2016.06.062
56. Jone PN, Tapia D, Davidson J, et al. (2015) Successful treatment of myocardial infarction in an infant with Kawasaki disease. *Semin Cardiothorac Vasc Anesth* 19: 255–259. https://doi.org/10.1177/1089253215573328

57. Garcia Verde MJ, Martinez Roca C, Yanez Gomez P, et al. (2016) Abciximab in refractory Kawasaki disease. *Eur J Hosp Pharm* 23: A33–A34. https://doi.org/10.1136/ejhpharm-2016-000875.76