TNF and IL-1 Targeted Treatment in Kawasaki Disease

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Opinion statement

Kawasaki disease (KD) is a multisystemic vasculitis affecting young children and the most common cause of acquired heart disease in children in the developed world. Current treatment recommendations for acute KD include IVIG and aspirin, but there are no evidence-based guidelines for children who do not respond to IVIG treatment. Widely applicable risk stratification algorithms to identify patients at high-risk of treatment failure and poor coronary artery outcome are not available. Over the past few years, increasing knowledge of the pathophysiology of disease have resulted in the identification of key inflammatory mediators and the use of biologic pathway targeting agents such as TNF and IL-1 inhibitors for children with IVIG-resistant disease. However, despite considerable efforts, adequately powered, randomized, controlled and prospective trials are lacking. In this review, we summarize the recent advances in our understanding of disease pathobiology and provide an overview of the currently available studies on anti-TNF and IL-1 therapy in KD.

Introduction

Kawasaki disease (KD) is an acute, self-limited, systemic vasculitis with predilection for coronary artery involvement and the most common cause of acquired heart disease in children from developed countries [1•]. KD affects mostly young children <5 years of age and presents as a multi-system inflammation characterized by prolonged fever, a polymorphous skin rash, induration and erythema of the hands and feet, oral mucosal

inflammation, non-exudative conjunctivitis and cervical lymphadenopathy. Epidemiologic studies and clinical observations suggest an infectious trigger: the clinical presentation similar to that in other infectious diseases, the seasonal clustering in winter and spring, temporal clusters of epidemics and the peak incidence between 6 months and 5 years of age [2–4]. Various etiologic agents including viruses, bacterial toxins and

superantigens have been associated with KD [5–7]. Although a single causative agent has not been linked to acute KD, an infectious trigger is thought to activate an abnormal immunologic response in genetically susceptible individuals [8].

The systemic immune response in KD encompasses both, the innate and adaptive immune system. Neutrophils and macrophages are involved in the early inflammatory response and release pro-inflammatory cytokines including IL-1 β , TNF α and IFN γ with, pleiotropic, down-stream effector functions. Both TNF α and IL-1 β have been associated with vascular endothelial cell damage and coronary artery lesions in acute KD [9]. Antigen presentation and co-stimulation lead to T cell activation with further significant increase of pro-inflammatory cytokine production. To date, recommendations for the treatment of acute KD consist of aspirin and intravenous immune-globulin (IVIG) [1•]. IVIG decreases the risk for coronary artery aneurysms formation from 25 to 5 %, in those appropriately treated [10•]. Approximately 20–30 % of children do not respond to standard treatment and develop persistent or recrudescing fever after a single dose of IVIG [11–13]. This subgroup of children has the highest risk to develop coronary artery lesions [1•]. Various predictors of poor outcome such as male gender, higher C-reactive protein, worse anemia, lower serum albumin and serum sodium have been included into different scoring systems to assess the severity of KD and the risk of IVIG resistance [14–16]. None have been widely accepted or valid outside of Japan. More recent treatment approaches aimed at early identification of these high-risk patients and those presenting with coronary artery lesions by escalation of the initial anti-inflammatory treatment [17, 18, 19••]. However, despite the use of risk stratification algorithms, these treatment approaches are often too late and coronary artery damage already present.

Upregulation of TNF α and IL-1 β and their associated downstream effector molecules have been shown to play crucial roles in the mediation of systemic inflammation and coronary artery damage in KD [9, 20]. Understanding of these underlying pathophysiologic mechanisms build the rationale for the more recent, biologic pathway-targeted therapeutic approaches, which we will discuss in this review.

Tumor necrosis factor alpha

TNF α is a prototypic pro-inflammatory cytokine, mainly produced by activated macrophages, although other cell

types including dendritic cells and T cells can also produce TNF α . TNF α levels in the serum/plasma are unstable [21–23]. The reliability and reproducibility of TNF α detection may be influenced by various factors including blood collection tubes, processing and storage conditions and the type of assay used, and these factors need be taken into account when evaluating TNF α measurements in the context of clinical research [21, 22]. The key role of TNF α in the mediation of inflammation during the acute phase of KD has been reported in several studies. Significantly elevated serum levels of TNF α and soluble TNF receptor have been demonstrated in children with acute KD [24, 25] and including those with coronary artery aneurysms [26]. A recent report found no difference in the TNF α levels of children with and without coronary artery aneurysms pre-IVIG treatment [27]. However, after IVIG treatment, TNF α levels increased in children who did not respond to IVIG and in those with coronary artery lesions, but they decreased in children without coronary involvement [27].

TNF α downstream effectors

In addition to TNF α itself, its downstream effector molecules are key players in the mediation of systemic inflammation and coronary artery damage [28–31]. TNF α signalling leads to nuclear translocation of NF- κ B and increased expression of various gene products. These include cell proliferation, leukocyte recruitment molecules, other pro-inflammatory cytokines, acute phase reactants and proteases, such as matrix metalloproteases (MMP) [32–34]. Several downstream effects of TNF α have been directly linked with systemic and local inflammation as well as coronary artery damage and are described in detail below.

TNF α -mediated leukocyte migration is necessary for coronary artery inflammation [28]. Leukocyte migration is a highly coordinated process that is regulated by chemokines and adhesion molecules and follows three steps: leukocyte rolling, firm adhesion and transendothelial migration [33, 35]. The interaction between vascular endothelium and leukocytes leads to a local inflammatory response. Increased expression of the chemokine RANTES and of adhesion molecules including ICAM-1 and E-selectin has been found in children with acute KD [36, 37]. The critical role of TNF α -mediated expression of leukocyte recruitment molecules has also been

demonstrated in a KD mouse model [28]. Hui-Yuen and colleagues reported that T cell activation leads to TNF α expression in the peripheral immune system [28]. This was followed by in situ production of TNF α in the coronary artery vessel wall, which coincided temporally and spatially with the presence of maximal lymphocyte infiltration into the coronary arteries. Persistent TNF α production and local immune response resulted in elastin degradation, vessel wall damage and the characteristic coronary artery lesions seen in KD. Interestingly, when TNF α activity was blocked, either by treatment with the TNF α inhibitor (etanercept) or by abolishing the TNF α signalling pathway by use of TNFRI knockout mice, local inflammation and elastic breakdown of the coronary arteries were ameliorated [28].

Increased expression of proteases, especially MMPs, is another important downstream product of TNF α signalling. MMPs are a family of proteolytic enzymes that are able to destroy the extracellular matrix by degradation of collagen and elastin fibers. MMPs are regulated at multiple levels and controlled by many factors, and among others by TNF α [38]. MMP-9 has been found to be localized to both coronary artery aneurysms and unaffected coronary artery segments of fatal human KD cases [39]. As MMP-9 was not expressed in coronary arteries from non-KD controls, the authors suggested that MMP-9 plays a critical role in the development of aneurysms in KD. The upregulation of MMP-9 expression by local inflammation and in situ production of TNF α has been demonstrated in a KD mouse model [29]. Abolishing the MMP-9 activity significantly reduced coronary artery lesions despite ongoing inflammation. MMP-9 appears to be a key downstream effector molecule, produced as a result of the local inflammatory response, and the critical link between inflammation and the coronary artery damage [29].

Production of pro-inflammatory cytokines is another key downstream effector function of TNF α important in the pathogenesis of KD. One of these pro-inflammatory cytokines is IL-6. IL-6 levels are elevated in KD patients and associated with various biologic effects including increased acute-phase proteins, T cell activation, procoagulant effects and thrombocytosis [40]. In addition, IL-6 can upregulate the production of MMP-9 through platelet activation [41].

Agents able to inhibit TNF α and/or its downstream effector functions such as TNF α inhibitors, or MMP inhibitors such as ulinastatin (a neutrophil elastase inhibitor), doxycycline (antibiotic with MMP inhibiting function) or novel MMP small molecule inhibitors have proven effective in preventing coronary aneurysms in pre-clinical disease models and offer promising treatment strategies in children with KD [28–31].

Interleukin-1 β

During the past few years, IL-1 β has been increasingly recognized to play a pivotal role in various diseases [42]; among them the recurrent fever syndromes in childhood, in which many have been found to be monogenic in origin leading to abnormal regulation of innate immunity [43, 44]. IL-1 β shares many biological functions with TNF α [45] and like TNF α , macrophages are the main source of IL-1 β production, but neutrophils, epithelial cells and endothelial cells are also able to produce IL-1 β . In comparison to TNF α , IL-1 β is more stable in the blood [21]. IL-1 β is synthesized as the inactive IL-1 β precursor that is enzymatically cleaved by caspase-1 releasing the active cytokine [46]. Caspase-1 is activated by the action of the inflammasome, a large intracellular multi-molecular complex. Clinical and animal studies have provided evidence for the critical role of inflammasome activation and IL-1 β production in KD. Maury et al. reported that serum levels of IL-1 β were significantly elevated in children with KD compared with age-matched healthy controls [20]. Investigation of gene-expression patterns in KD patients revealed an increased relative abundance of gene transcripts associated with innate immune and pro-inflammatory response, including the IL-1 β gene [47]. Increased IL-1 β gene expression and diminished IL-1RA expression have been demonstrated in IVIG resistant patients [48]. An association of IL-1 β polymorphism resulting in increased IL-1 β secretion and IVIG resistance has recently been reported [49]. These data are further supported by observations that IVIG treatment in children with KD is associated with a reduction of IL-1 β secretion (in vivo) and that IVIG is able to downregulate IL-1 β and to upregulate IL-1RA production in vitro [50–52].

More recently, a possible link between a single nucleotide polymorphism and increased IL-1 β production has been suggested. A genome-wide association study discovered a single nucleotide polymorphism in the inositol 1,4,5-triphosphate 3 kinase (ITPKC) gene, which was

associated with increased risk of KD and development of coronary artery aneurysms [53]. ITPKC negatively regulates the intracellular Ca^{2+} influx that plays a crucial role in the NLRP3 inflammasome activation. The single nucleotide polymorphism in the ITPKC gene results in a sustained elevation of intracellular Ca^{2+} and thus in an increased NLRP3-inflammasome activation leading to IL-1 β production. These mechanisms provide a possible link between the single nucleotide polymorphism in the ITPKC gene and KD [54–56]. A large genomic study investigated whole blood transcriptional profiles of 146 acute KD subjects compared to non-KD pediatric patients and also revealed the importance of the IL-1 related pathways in children with KD [57•].

The role of IL-1 β in the induction of coronary artery inflammation has recently been further elucidated in a mouse model of KD. Lee and colleagues demonstrated that IL-1R-deficient mice and caspase-1-deficient mice are not affected by coronary arteritis indicating the key role of IL-1 β in the pathogenesis of coronary artery lesions [58]. Additionally, treatment with IL-1RA significantly blocked development of coronary artery lesions and it decreased overall myocardial inflammation [58]. While anti-TNF therapy was also able to prevent coronary artery lesions, it did not reduce the incidence of myocarditis in the animal model. Taken together, IL-1 blockade showed a

trend towards more effective inhibition of coronary artery damage and myocarditis compared to TNF blockade in this murine model of KD [58]. The same group reported that both IL-1 β and IL-1 α are essential for the development of coronary arteritis in the same KD mouse model and concluded that therapeutic agents should target both IL-1 α and IL-1 β [59].

IL-1 β downstream effects

IL-1 β regulates the transcription of several downstream effector molecules resulting in its pleiotropic effects. IL-1 β is the most pyrogenic of the fever-inducing cytokines and stimulates the bone marrow leading to a release of neutrophils [60]. Similar to TNF α , IL-1 β is able to activate inflammatory processes and the production of IL-6, which likely accounts for the rise in acute-phase proteins and thrombocytosis [61]. IL-1 β signalling is regulated through type I IL-1 receptor. Either natural IL-1 receptor antagonist (IL-1RA) or the therapeutic recombinant molecule (anakinra) can block IL-1 receptors and prevent normal IL-1 signalling [62]. Therapeutic IL-1 blockade has been successfully used in murine model of KD [58, 59, 63, 64] and by the KD community for treatment of treatment resistant KD.

Treatment

Inhibition of TNF α

A few case series and small clinical trials have reported potential beneficial effects of TNF blockade in children with KD (Table 1). Beneficial effects were observed specifically regarding duration of fever, length of hospital stay and normalization of acute phase reactants after a single dose of infliximab in children who failed IVIG [10•, 65]. However, none of them reported improved coronary artery outcome with the use of infliximab [10•, 65, 66]. A retrospective study evaluated the use of a single infliximab infusion (5–10 mg/kg) in children resistant to at least two doses of IVIG [67]. Treatment response, measured as defervescence of fever was observed in 13/16 children. CRP levels were elevated in all except one child prior to the infliximab infusion, and CRP levels decreased after infliximab in all 10 children in whom it was re-measured within 48 h of treatment. Infliximab treatment was reported to be safe and well tolerated [67]. A small multicenter, randomized, prospective trial compared IVIG infusion (2 g/kg) to infliximab (5 mg/kg) in 24 children with KD refractory to a single dose of IVIG [66]. Four of the 13 children (31 %) randomized to a second IVIG infusion required additional therapy with infliximab, while 3/16 children (19 %) who received infliximab as either second- or third-line treatment

Table 1. Anti-TNF treatment for treatment refractory Kawasaki disease

TNF blockade in IVIG-resistant KD				
Study	Burns et al. 2005 [67]	Burns et al. 2008 [66]	Son et al. 2011 [65]	Mori et al. 2012 [68]
Study type	Retrospective case series	Multicenter, randomized, prospective trial	Retrospective two-center study	Open-label case series
Number of patients	17	24	106	20
Age (range)	Median 2.6 y (0.12–13.1 y)	IVIG: median 22 m (10–38 m) IFX: median 20 m (8–37 m)	IVIG: median 23 m (9–36 m) IFX: median 29 m (15–57 m)	Mean 4.6 y (1.9–10.5 y)
Gender (M/F)	11/6	17/7	69/37	10/10
Treatment protocol	Children refractory to IVIG: IFX 5 mg/kg (one dose): $n = 15$ or 10 mg/kg: $n = 2$	Children refractory to IVIG: IFX 5 mg/kg (one dose): $n = 12$ or 2nd IVIG 2 g/kg: $n = 12$	Children refractory to IVIG: IFX 5 mg/kg (one dose): $n = 20$ 2nd IVIG (2 g/kg): $n = 86$	Children refractory to IVIG: IFX 5 mg/kg (one dose), plasma exchange for children refractory to IFX
Study results	Cessation of fever in 81 % of children, decrease of CRP levels in 10/10 children in whom it was measured	No significant differences in duration of fever or laboratory parameters between the two treatment groups	Significantly fewer days of fever (median 8 vs 10 days, $p = 0.028$) and shorter hospitalization (median 5.5 vs 6 days, $p = 0.040$) in the IFX group	Rapid defervescence and improvement of clinical/laboratory findings in 90 % of children 2 children were refractory to IFX and underwent plasma exchange
Coronary artery abnormalities	12 children with coronary artery abnormalities before IFX therapy	No significant difference in coronary artery outcome between the two groups	No significant difference in coronary artery outcome between the two groups	Coronary abnormalities regressed 19/20 children One child presented coronary artery lesions at 30 days after treatment onset, complete regression was noted 1 year later
Complications/adverse events	IFX was safe and well tolerated	IFX was safe and well tolerated	Similar rate of adverse events between the two treatment groups	IFX was safe and well tolerated

IFX infliximab, IVIG intravenous immunoglobulins, ASA acetyl salicylic acid, IQR interquartile range, y years, m months, CRP C-reactive protein, ESR erythrocyte sedimentation rate

required additional medication. No significant differences were observed between the treatment groups in time until defervescence, change of laboratory variables and coronary artery abnormalities reported as body surface area normalized z-scores. Five children developed coronary artery aneurysms (four randomized to infliximab and one to IVIG), however in four of them coronary artery abnormalities were already present at study entry. Infliximab appeared well tolerated and no serious adverse events were attributed to the treatment [66]. In a more recent retrospective review of IVIG-resistant KD, treatment with infliximab ($n = 20$ children) was associated with fewer days of fever (median 8 vs. 10 days; $p = 0.028$) and shorter hospitalization (median 5.5 vs. 6 days, $p = 0.040$) compared to re-treatment with IVIG ($n = 86$ children). The rates of coronary artery aneurysms and adverse events were similar in both treatment groups [65]. It is unclear whether the patients in the previous retrospective study [66] were a subset of the patients reported in the second retrospective study [65]. Mori and colleagues treated 20 Japanese children who had failed IVIG with infliximab 5 mg/kg in an open-label trial [68]. Eighteen children showed a rapid decrease of fever (within 24 h) as well as decrease of the number of inflammatory symptoms and normalization of the inflammatory markers within 3 days after infliximab. Two patients required plasma exchange to prevent coronary artery damage, as they were refractory to infliximab. Coronary abnormalities including increased echogenicity and mild dilatation were noted in all patients at baseline and regressed in all but one child within 30 days after therapy. One child progressed to develop a coronary artery aneurysm at 30 days, but had a complete regression of the coronary artery lesion 1 year later. There were no reports of adverse events [68]. Another study investigated the dynamic changes of cytokines during infliximab treatment in children with KD [69]. Although serum levels of proinflammatory cytokines decreased dramatically after infliximab, markers of local tissue damage were not suppressed. In contrast, successful IVIG treatment markedly decreased all measured soluble mediators of inflammation. The authors concluded that proinflammatory cytokines and markers of local tissue damage respond differently to infliximab and suggested that infliximab is effective for suppression of systemic cytokine-mediated inflammation, but could not completely inhibit local inflammation at the coronary arteries [69]. The findings regarding systemic inflammation are supported by recent data showing that levels of TNF α and many other proinflammatory mediators decreased in IVIG-resistant children who responded to infliximab, whereas they did not decrease in infliximab non-responders [70]. In particular, IL-6 and IL-10 were insufficiently suppressed in non-responders. The authors suggested that inflammatory mechanisms other than the TNF α pathway are at play in infliximab-refractory children.

Anti-TNF agents have also been investigated for intensification of primary therapy in KD (Table 2) [10•, 71]. In a phase 3, randomized, double-blind, placebo-controlled trial comparing IVIG to IVIG plus infliximab (5 mg/kg), the addition of infliximab did not significantly reduce treatment resistance nor improve coronary artery outcome, although the trial was underpowered for this endpoint [10•]. However, the IVIG + infliximab group had shortened duration of fever and more rapid reduction of

Table 2. Anti-TNF treatment for primary treatment of Kawasaki disease

TNF blockade for primary treatment of KD		
Study	Tremoulet et al. 2014 [10•]	Choueiter et al. 2010 [71]
Study type	Phase 3, randomized, double-blind, placebo-controlled trial	Prospective open-label trial
Number of patients	198	15
Age (range)	IFX: median 3.0 y (IQR 1.9–4.8 y) Placebo: median 2.8 y (IQR 1.8–4.2 y)	Mean 2.6 y (9 m–4.8 y)
Gender (M/F)	121/75	8/7
Treatment protocol	Standard therapy (IVIG 2 g/kg + ASA 80–100 mg/kg) PLUS IFX 5 mg/kg (single dose) or standard therapy PLUS placebo	Standard therapy (IVIG 2 g/kg + ASA 80–100 mg/kg) PLUS ETN 0.4–0.8 mg/kg at day 1, 7, and 14 after IVIG
Study results	Fewer days of fever (median 1 vs 2 days, $p < 0.0001$), greater mean reduction of CRP ($p = 0.0003$) and absolute neutrophil count ($p = 0.024$) at 24 h after treatment and of ESR ($p = 0.09$) at 2 weeks No significant difference at 5 weeks after treatment	Defervescence in all children Normalization of CRP at day 7 in all children
Coronary artery abnormalities	Greater decrease in Z score of left anterior descending artery ($p = 0.045$) at week 2 after treatment, but no significant difference at week 5 No significant difference for the proximal right coronary artery Z score at any time point	No new coronary artery aneurysm/dilatation or cardiac dysfunction observed during study period Five children had coronary artery lesions at baseline, in 3/5 decrease of the z-score was observed within 6 weeks, 1/5 resolution of the aneurysms was seen at 6 months
Complications/adverse events	Infliximab was safe and well tolerated	ETN was safe and well tolerated

IFX infliximab, ETN etanercept, IVIG intravenous immunoglobulins, ASA acetyl salicylic acid, IQR interquartile range, y years, m months, CRP C-reactive protein, ESR erythrocyte sedimentation rate

inflammation [10•]. Intensified primary treatment with IVIG and etanercept (0.8 mg/kg weekly for three doses) has been reported to be safe and well tolerated in 15 children with KD [71]. Another, larger multicenter, double-blind, randomized and placebo-controlled trial assessing the efficacy of etanercept in addition to IVIG in acute KD is currently in progress (NCT00841789).

There are several concerns related to the use of TNF inhibitors in children with KD, chief among them infection and malignancy. The risk-benefit profile of TNF inhibitors in the early, acute phase of KD is unclear. Infectious agents responsible for triggering KD are commonly still present during acute KD [72], and active infections are a contraindication to the use of TNF inhibitors. In refractory disease, where the exaggerated immune response as opposed to the infectious agent, likely drives the inflammatory response,

the benefits may outweigh the potential infectious risk. The risk of malignancy after a single dose of infliximab as used in most of the children with KD is not known. Additionally, various other concerns regarding the use of TNF blockade in children with KD remain unsolved: there is a lack of clear dose recommendations for infants and children, absence of long-term safety data and paucity of treatment efficacy in preventing coronary artery aneurysms. Future prospective, randomized clinical trials are needed to clarify the role and efficacy of TNF blockers as primary and rescue treatment of KD.

Besides TNF inhibition, treatment approaches have been directed towards the TNF α -mediated downstream effects with MMP-9 and associated elastolytic activity as one such potential therapeutic target. Ulinastatin, a neutrophil elastase inhibitor, has been associated with better treatment response and reduced coronary artery lesions when used as therapeutic agent together with IVIG and aspirin [73]. Ulinastatin is recommended as second-line treatment in Japan for IVIG-resistant KD [74•]. Other MMP inhibitors found to be effective in pre-clinical models of KD have also moved to the bedside [30, 76]. The efficacy and safety of doxycycline, an antibiotic with MMP inhibiting function, is currently evaluated in a small pilot study in KD children with coronary artery lesions (NCT01917721). Atorvastatin, a 3-hydroxy-3-methylglutaryl (HMG) coenzyme A (CoA) reductase inhibitor and commonly used lipid lowering agent, also has anti-inflammatory and endothelial-healing properties that may improve coronary artery outcome [75]. Atorvastatin has been shown to inhibit TNF α -mediated MMP-9 production and to reduce T cell activation in pre-clinical models [75, 76]. Based on these findings, Atorvastatin is currently investigated in two studies including children with coronary artery abnormalities secondary to KD (NCT01431105, NCT02114099).

Inhibition of IL-1 β

To date, two case reports have been published reporting the successful use of anakinra, an IL-1 receptor antagonist inhibiting both IL-1 α and IL-1 β , in children with refractory KD [63, 64], but many more cases of treatment resistant disease receiving IL-1 blockade have been reported in online discussions. Cohen et al. reported a 2-year-old boy with severe, relapsing KD, who responded twice to anakinra [63]. The boy relapsed and his clinical and coronary findings rapidly deteriorated after discontinuation of anakinra. When the IL-1 blockade was restarted, he rapidly improved. Interestingly, the coronary artery aneurysms, which had progressed to giant aneurysms, normalized by 6-month follow-up suggesting a potential beneficial role of IL-1 blockade in vascular injury/remodelling [63]. Shafferman and colleagues reported an 11-week-old female with KD complicated by macrophage activation syndrome refractory to IVIG and high-dose glucocorticosteroids [64]. Anakinra was instituted due to high suspicion for macrophage activation syndrome and a dramatic clinical improvement was observed, but repeat echocardiography revealed diffuse enlargement of the entire coronary artery system and one dose of infliximab was given in addition to anakinra and corticosteroids. Corticosteroids and anakinra were tapered off during the next 5 months. Repeat echocardiography at 8-month follow-up revealed significant improvement with only

mild dilatation [64]. Recent discoveries supporting the role of IL-1 in KD have led to two phase 2 clinical trials for anakinra in IVIG-resistant KD children (NCT02179853, NCT02390596).

Overall, IL-1 blockade has a good safety profile [77–79]. Similar to all biologics suppressing the immune system, the risk for pathogenic bacterial infections increases with IL-1 blockade; however, the occurrence of opportunistic infections is rare [77]. Even though there are no reports indicating an increased risk for malignancy with IL-1 blockade, the effects of long-term anti-IL-1 therapy on the natural defenses against malignancies are unknown [77]. As with TNF inhibition, the optimal dosage and treatment protocol remains to be determined and long-term safety data are lacking. The results of the ongoing clinical trials are awaited eagerly and may clarify some of these questions.

Conclusions

Lessons learned from pathobiology have identified TNF α and IL-1 β as important mediators of inflammation in KD. Mechanistic studies in pre-clinical models of disease partnered with clinical correlates in affected children strengthen the evidence from the bench to the bedside. Clinical use of biologic agents targeting these two soluble mediators of inflammation in children with IVIG-resistant disease is widespread, but despite considerable efforts, adequately powered, randomized, controlled and prospective trials are lacking. Beneficial effects for TNF blockade on shortening fever duration, length of hospitalization and decreasing biochemical markers of inflammation have been described in small case series and clinical trials, but no significant effect is seen on coronary outcome. The use of therapeutic agents to inhibit TNF-mediated elastolysis is part of standard therapy in some countries and has ongoing trials in others. The identification of an IL-1 β signature in KD is more recent as is the use of IL-1 inhibitors in the clinical setting. Only case reports exist in the literature, but several clinical trials are underway to assess their efficacy in treatment of recalcitrant disease and to assess the effect on coronary outcome in addition to duration of fever. International collaborations have been the cornerstone of our expanding knowledge of unique molecular signatures in children with KD. This same spirit of collaboration is needed to adequately power clinical trials that will define the therapeutic applications, so that as our understanding of pathobiology increases, so too will the precision of our treatment decisions.

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Compliance with Ethical Standards

Conflict of Interest

Florence A. Aeschlimann declares that she has no conflict of interest.

Rae S. M. Yeung declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent

With regard to the authors' research cited in this paper, all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. In addition, all applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

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- Of major importance

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