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Found in Translation: International initiatives pursuing interleukin-1 blockade for treatment of acute Kawasaki Disease

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Abstract

The decision to move forward with three clinical trials of IL-1 blockade for treatment of acute Kawasaki disease is a case study in translational science. These trials were born on the one hand from transcriptome studies of host response during the acute disease coupled with animal model investigations of key immune signaling pathways and, on the other hand, out of clinical desperation to intervene in patients with severe inflammation in the setting of acute Kawasaki disease. The convergence of laboratory science and clinical observations led to the clinical trials described here and serves as a model for how such observations can be translated into new therapies.

Keywords

vasculitis; interleukin-1; coronary artery aneurysms; pediatrics; autoinflammatory disease; Kawasaki disease

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The successful translation of bench research into clinical practice requires physician scientists who understand both the unmet clinical needs as well as the experimental gaps in knowledge. In the case of Kawasaki disease (KD), a self-limited vasculitis of unknown etiology and the most common cause of acquired heart disease in children, communication between research teams achieved the necessary coalescence of science and clinical medicine to rapidly translate experimental mouse experiments and human transcriptomic data and into three separate clinical trials on two continents. What follows is a story of how research teams in the Europe and the U.S. capitalized on experimental findings to devise clinical

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trials to test a new paradigm: KD is a systemic inflammatory condition in which activation of the IL-1 signaling pathway is an essential driver of disease pathogenesis.

The current understanding of KD is that an immunologic reaction is elicited in genetically susceptible hosts upon exposure to the KD trigger or triggers, which are thought to be stimuli that enter through the upper respiratory tract (1). Both mystery and controversy surround the exact nature of the trigger with some groups advocating a novel virus and others suggesting an antigenic exposure without an infectious agent. The subset of KD children who suffer damage to the coronary arterial wall (2–4) and aneurysms in these vessels comprise only 25% of total population of KD-susceptible children(5). Therapy with intravenous immunoglobulin (IVIG) reduces the prevalence of aneurysms to 3–6% and rates of aneurysms are highest among patients who fail to become afebrile after the first dose of 2g/kg of IVIG (6, 7).

The mechanism by which IVIG reduces inflammation in the majority of patients is only now being elucidated despite the widespread clinical use of this treatment for over three decades. *In vitro* studies have documented that IVIG increases IL-1R antagonist expression in human monocytes, which may be relevant in KD (8). Recent immunologic studies have established that secretion of IL-10 by tolerogenic myeloid dendritic cells (mDC) and natural regulatory T cells (nTreg) is a critical event in down regulation of inflammation in acute KD(9, 10). Incubation of peripheral blood mononuclear cells with the constant region of the IgG molecule (Fc) *in vitro* leads to the expansion of a population of Fc-specific nTreg and mDC and to increased secretion of IL-10. Immune monitoring of patients at the subacute stage has established that these populations expand after IVIG treatment *in vivo* (10). However, patients who develop coronary artery aneurysms (CAA) have a reduced capacity to expand these populations due to mechanisms that are currently under study. Other mechanisms of action of IVIG in KD that lead to the very rapid downregulation of systemic signs of inflammation have yet to be elucidated.(11) Clinicians who care for acute KD patients have been aware of the need for adjunctive therapies that could be used with IVIG to reduce inflammation in the subsets of patients with early aneurysms, severe myocarditis, and in those who had persistent fever following IVIG infusion.

Role of TNFα in acute KD

The pro-inflammatory cytokine TNFα was known to be markedly elevated during the acute phase of KD and levels were highest in patients who developed CAA(12). Thus, it was a logical choice to try TNFα inhibition with infliximab following the approval of this monoclonal antibody for pediatric patients with inflammatory bowel disease in 2006. After publications reporting the compassionate use of infliximab for IVIG-resistant KD patients, the results of the first proof of concept trial were published in 2008 (13–16). This trial enrolled 24 acute KD subjects who had persistent fever 36h after completion of their IVIG infusion and randomized them to either second IVIG infusion or infliximab 5mg/kg. The results were promising with 11 of the 12 subjects randomized to infliximab becoming afebrile and not requiring further treatment compared with eight of the 12 subjects who received a second infusion of IVIG. There was no adverse outcome signal and the pharmacokinetics of the antibody appeared to be similar to adult studies. However, clinicians

realized that waiting until a patient had failed therapy to initiate additional treatment left the patient with unchecked inflammation for a prolonged period and put the coronary arteries at risk from on-going destructive processes. The shift in interest then focused on intensification of initial IVIG therapy to more rapidly bring inflammation under control.

Clinical trials of intensification of initial therapy

Three sentinel trials that attempted to identify adjuvant therapies that could benefit KD patients took place in the U.S. and Japan. In the Pediatric Heart Network trial of a placebo-controlled, randomized study of a single IV dose of methylprednisolone (30 mg/kg) plus standard therapy (IVIG plus aspirin), no difference was seen in the coronary artery outcome or rate of IVIG resistance (17). In the Japanese RAISE trial, KD patients at greatest risk of IVIG resistance and CAA were selected using a clinical scoring system that had been validated in the Japanese population, but had shown poor predictive performance for U.S multiethnic KD patients (7, 18, 19). Japanese subjects were randomized to either IV followed by oral methylprednisolone (2 mg/kg) or placebo in addition to IVIG and aspirin and were treated with study drug for approximately three to five weeks. Results showed a significant reduction in IVIG resistance and coronary artery Z score (internal diameter of the coronary artery normalized for body surface area and expressed as standard deviations from the mean) between the groups in favor of steroids. In a U.S. trial of intensification of initial therapy with TNFα blockade, unselected KD patients were randomized to a single dose of infliximab (5 mg/kg) or placebo in addition to IVIG and aspirin (20). Results showed a significant reduction in measures of inflammation, coronary artery Z score, and duration of fever. However, addition of infliximab to initial IVIG therapy failed to prevent IVIG resistance. Current evidence supports the use of infliximab as rescue therapy for patients with IVIG-resistance, but trials have not evaluated its use as adjunctive therapy in patients with early evidence of coronary artery damage.(21) Although some benefit was demonstrated in each of these trials, there remained highly resistant KD patients whose course was not altered by either steroids or TNFα blockade and whose arteries underwent progressive damage despite timely treatment. Thus, clinicians were aware of an unmet clinical need to devise specific and more effective therapies for this subset of patients.

Interleukin-1 (IL-1) as a master cytokine

IL-1 is a central mediator of innate immunity and inflammation and is considered a master cytokine of local and systemic inflammation (22). IL-1α and IL-1β are encoded by distinct genes, bind to the same receptor (IL-1R1), and have similar biological properties. IL-1β mediates the unchecked inflammation in many autoinflammatory diseases (23). IL-1β also enhances antigen-driven CD8+ T cell differentiation, proliferation, memory, and migration into tissues (24). This is important with respect to the pathogenesis of acute KD as CD8+ T-cells infiltrate the coronary artery wall and likely contribute to a destructive process associated with aneurysm formation (25).

IL-1β is transcribed as an inactive precursor that requires assembly of the NLRP3 inflammasome to activate caspase 1, the enzyme that cleaves pro-IL-1β to release the biologically active form of the cytokine. In contrast, the IL-1α precursor is functional and

when released from necrotic cells in a site of injury can bind to the IL-1R1 of neighboring cells, thus initiating a cascade of inflammatory cytokines and chemokines (26). Circulating IL-1α is rarely detected in patient sera but is found within endothelial cells and apoptotic bodies released from these cells. (27).

The relative contributions of IL-1α and β to the vasculitis of KD have yet to be defined. It is intriguing that IL-1β signaling prolongs neutrophil survival and drives proliferation of smooth muscle cells (SMC) and myofibroblast formation (28–31), all pathologic hallmarks of the arteriopathy seen in KD(32, 33). IL-1 induced SMC proliferation is driven by matrix metalloproteinases, including MMP3 and MMP9, both of which are implicated in human KD (30, 34–38). Indeed, SMC-derived myofibroblasts can actively proliferate in an uncontrolled fashion in the arterial wall after KD leading to luminal myofibroblastic proliferation (LMP), which can progress to life-threating coronary artery stenosis and infarction (39). Although therapies are available to reduce risk of thrombosis in CAA, no therapies have been tested to reduce LMP, which can lead to myocardial ischemia. IL-1α signaling may be responsible for amplifying inflammatory cell infiltration into the arterial wall in regions of vascular SMC and endothelial cell necrosis.

Experience with IL-1 blockade in pediatric inflammatory diseases

Cryopyrin-associated periodic fever syndrome (CAPS) is the only disease with FDA and EMA approval for anakinra in infants (≥8 months, and 10 kg), but anakinra is widely used off-label in systemic autoinflammatory and autoimmune syndromes in children including systemic juvenile idiopathic arthritis (sJIA), macrophage activations syndrome, colchicine-resistant familial Mediterranean fever (FMF) and idiopathic pericarditis, and TNFα receptor-associated periodic syndrome (TRAPS), (40–44). In a recent study of 26 patients with the autoinflammatory syndrome neonatal-onset multisystem inflammatory disease (NOMID), treatment with anakinra for 36 months had a low adverse event rate, with upper respiratory infection as the most commonly reported complication (45). A similar study using anakinra in another CAPS phenotype, Muckle-Wells syndrome, did not demonstrate any serious adverse events in the 12 patients treated with anakinra, of whom 5 were children (46). In most of these studies in young children, the dose of anakinra needed to achieve complete anti-inflammatory effect was between 4 and 10mg/kg/day.

Canakinumab is a selective monoclonal antibody against IL-1β with a long half-life of 22 days (47). In patients with CAPS, a single subcutaneous dose of 2mg/kg for pediatric patients and 150 mg in adult patients every eight weeks provided rapid resolution of clinical and biological signs of inflammation (48). Younger patients and those with the most severe phenotypes require higher doses (or shorter intervals between doses). The use of subcutaneous doses of 2 mg/kg of canakinumab every 8 weeks for 24 weeks was associated with complete control of clinical manifestations and laboratory parameters in patients with a Muckle Wells syndrome phenotype, but those who were younger or manifested more of a chronic infantile neurological, cutaneous and articular (CINCA) syndrome phenotype needed higher or more frequent dosing (49). In sJIA, the approved dose is 4mg/kg every 4 weeks (50).

Specific inhibitors of IL-1α have not been tested in pediatric inflammatory diseases. It is intriguing that a human antibody specific for IL-1α, MABp1, is now in early clinical trials for different advanced cancers in adultsand has improved survival and well-being of patients. (51) The availability of selective IL-1 blocking agents will further our understanding of the relative roles of IL-1α and β in different diseases involving both local and systemic inflammation.

Insights from KD genetic studies: Calcium signaling and the IL-1 pathway

Genetic studies have identified several risk alleles that influence both susceptibility to KD and development of CAA (52). Among these, a functional polymorphism in the inositol 1,4,5-trisphosphate 3-kinase C (ITPKC) gene was reproducibly associated with KD susceptibility and CAA across diverse populations (53–56). Another polymorphism that influenced KD susceptibility was private to the Japanese population and was located the ORAI1 gene that encodes for a calcium channel (57). Importantly, both the ITPKC and ORAI1 genes regulate calcium flux in the cell, and these polymorphisms lead to sustained elevation of intracellular Ca^{2+}, which can both induce NLRP3 inflammasome activation and secretion of biologically active IL-1β as well as the release of IL-1α (58–61).

Insights from KD proteomic and transcriptomic studies: Role of IL-1 in acute KD

Several observations suggested that IL-1plays an important role in KD vasculitis. In children with KD, the IL-1 pathway is upregulated compared to pediatric febrile controls, as demonstrated by increased transcript abundance by microarray and by increased levels of pathway proteins in the plasma (62–66). Early studies determined that IVIG treatment was associated with a reduction in IL-1β secretion by peripheral blood mononuclear cells from KD patients with no CAA as compared to persistently elevated levels in IVIG-treated patients with CAA(63). In a microarray study of acute and convalescent whole blood samples collected in PAXgene® tubes from 146 KD subjects, KD transcript abundance profiles were compared to pediatric subjects with different acute infectious diseases and to pediatric healthy controls (65). Differentially expressed transcripts were analyzed according to their participation in different biologic pathways. Common features of the top three pathways for KD were the abundance of transcripts related to the NLRP3 inflammasome, IL-1α and β, and caspase-1. The upregulation of key genes in the IL-1 pathway was confirmed using qRT-PCR in an independent cohort of 20 KD patients and 10 healthy controls (65). In a different microarray study, IVIG-resistant KD patients, when compared to IVIG-responsive patients, had increased expression of the following IL-1 pathway genes: IL-1R1, IL-1R2, IL-1R associated kinase 3 (IRAK3), and TIFA and decreased expression of IL-1Ra (66).

Insights from the KD vasculitis mouse model: Role of IL-1 signaling

The limited availability of tissue samples from patients with KD has significantly impeded progress in understanding the etiology and pathogenesis of the disease, thus making the availability of a relevant animal model extremely valuable. A well-described mouse model

of coronary arteritis closely mimics the important histological as well as immune-pathological features of the cardiovascular lesions of acute KD (67–69). A single intraperitoneal injection of a cell wall extract from *Lactobacillus casei* (LCWE) reproducibly induces proximal coronary arteritis that is histologically similar to the coronary arteritis observed in human KD. In the LCWE mouse model, a subacute coronary arteritis with luminal myofibroblast proliferation (LMP) and stenosis mimics the lesions found in human arteries(70).

The mouse model of KD vasculitis is also associated with systemic inflammation and increased body temperature. Intact TLR2 and IL-1R signaling via MyD88 is required for this LCWE-induced vasculitis (71, 72). Moreover, this KD mouse model also predicts efficacy of treatment in children with KD. Currently used treatments in humans such as IVIG and anti-TNFα antibodies, have been shown to be beneficial in preventing coronary arteritis and aortitis in the LCWE-induced KD vasculitis mouse model (73, 74).

Using this model, Arditi and colleagues demonstrated the key role of IL-1 signaling pathways in the LCWE-induced mouse vasculitis model (75). Anakinra also prevented LCWE-induced abdominal aortic dilation and aneurysms (76). Of interest, anakinra was even more effective than IVIG or TNF-α blockade in reducing LCWE-induced myocarditis and improved heart function (ejection fraction) measured using a small animal MRI (70, 72). Thus, genetic and transcriptomic data from KD patients and data from the experimental mouse model of KD vasculitis have converged on the likely role of IL-1 signaling in the pathogenesis of KD vasculitis (Figure).

As the use of IL-1 blockade became more widespread for control of a diverse array of inflammatory conditions, clinicians were emboldened to try to IL-1 blockade in the treatment of desperately ill KD patients. In the first report of such use, Kuijpers and colleagues reported treatment of an infant with uncontrolled inflammation and giant aneurysms who finally responded to IL-1 blockade with anakinra after failing multiple other anti-inflammatory therapies (77). The patient experienced a dramatic clinical improvement but required prolonged treatment with anakinra. Subsequently, another severe KD patient who was resistant to IVIG treatment was treated with anakinra, which was well-tolerated and associated with resolution of systemic and coronary artery inflammation (78). So a convergence of genetic and genomic studies with experimental animal data and human clinical data set the stage for further investigation. The body of evidence supporting the importance of the IL-1 pathway in KD pathogenesis was now compelling enough for the launch of three different clinical trials of IL-1 blockade for treatment of acute KD.

Pediatric trials of IL-1 blockade in acute Kawasaki disease

There are currently three clinical trials of IL-1 blockade that enrolling patients with KD in Western Europe and the U.S. (Table 1).

Kawakinra trial (Europe)

The Kawakinra trial (Eudract Number: 2014-002715-41) is a Phase IIa, single dose, multi-center trial of anakinra in Europe. The primary objective is to assess the efficacy and safety

of anakinra in patients with IVIG-resistant KD. The secondary objectives are to assess the effect of anakinra on disease activity, coronary artery Z score, and changes in gene expression and protein levels of inflammatory biomarkers. Eligible patients are those aged eight months (10 Kg) to 18 years with a diagnosis of acute KD according to American Heart Association (AHA) criteria, and who have persistent or recrudescent fever at least 48 hours after the initiation of the IVIG infusion. After parental informed consent, subjects enter the screening period between the fourth to the thirteenth day of fever. Subjects enter the treatment phase if they develop recrudescent fever and receive a first dose of 2 mg/kg of anakinra subcutaneously. In case of fever persistence or recrudescence within 24h after the first dose, the next dose is increased to 4mg/kg. Persistence or recrudescence of fever within 24h is followed by a further increase to 6mg/kg. If a subject fails to respond within 48h at a dose of 6mg/kg, alternative treatment is administered at the center PI's discretion. The highest daily dose of anakinra (from 2–6mg/kg) is continued to complete 14 days of treatment.

ANAKID Trial (USA)

This is a Phase I/IIa dose escalation study to determine the safety, tolerability, and pharmacokinetics (PK) of anakinra in acute KD (clinicaltrials.gov # NCT 2179853)(79). Study eligible subjects are KD patients meeting AHA criteria who are within the first 20 days after fever onset, at least eight months of age, and have a Z score ≥3.0 for the right coronary artery (RCA) or left anterior descending coronary artery (LAD). All subjects will receive at least two weeks of therapy. Only subjects with an echocardiogram at two weeks that shows either an RCA or LAD Z score ≥ 2.5 or an aneurysm (≥ 1.5 × the adjacent segment) of one of the coronary arteries will complete a six-week course of anakinra. All subjects will remain on study for the full 6 weeks whether or not they are receiving anakinra.

Canakinumab Trial (Europe)

This is an industry-sponsored, Phase II multi-center trial in seven countries that is open for enrollment. The trial has two treatment arms and will enroll not only IVIG-resistant subjects, but also treatment-naïve subjects with complete KD diagnosed early in the course of their disease who will receive canakinumab as initial monotherapy. Treatment-naïve subjects will receive a single 6 mg/kg intravenous dose of canakinumab. The primary outcome measure will be the presence or absence of fever after drug administration. Subjects who respond with complete fever resolution will not receive IVIG, and may be selected to receive one or two follow-up subcutaneous injections at 4 and 8 weeks depending on the CRP level and clinical follow-up. If the subject remains febrile at 48–72h after the initial canakinumab dose, then the subject will receive the standard 2g/kg IVIG.

A second canakinumab treatment arm will enroll IVIG-resistant subjects with KD who have failed to become afebrile following one or two IVIG infusions. Subjects in this arm will receive the same initial canakinumab IV dose and a second and third dose of canakinumab at 4 weeks and 8 weeks after their initial study treatment.

Conclusion

The convergence of human genetic and transcriptomic data from KD patients with animal experimental data from the LCWE KD mouse model has led to three Phase I/II clinical trials that should rapidly determine the safety and tolerability of IL-1 blockade in the treatment of KD. The simultaneous testing of different entrance criteria (persistent fever, CAA, or uncomplicated treatment-naïve KD), different endpoints (body temperature, coronary artery status by echocardiogram), and different study medications (anakinra, canakinumab) will accelerate our understanding of the role of IL-1α and β in KD pathogenesis and the benefits and risks of IL-1 blockade in these diverse study populations.

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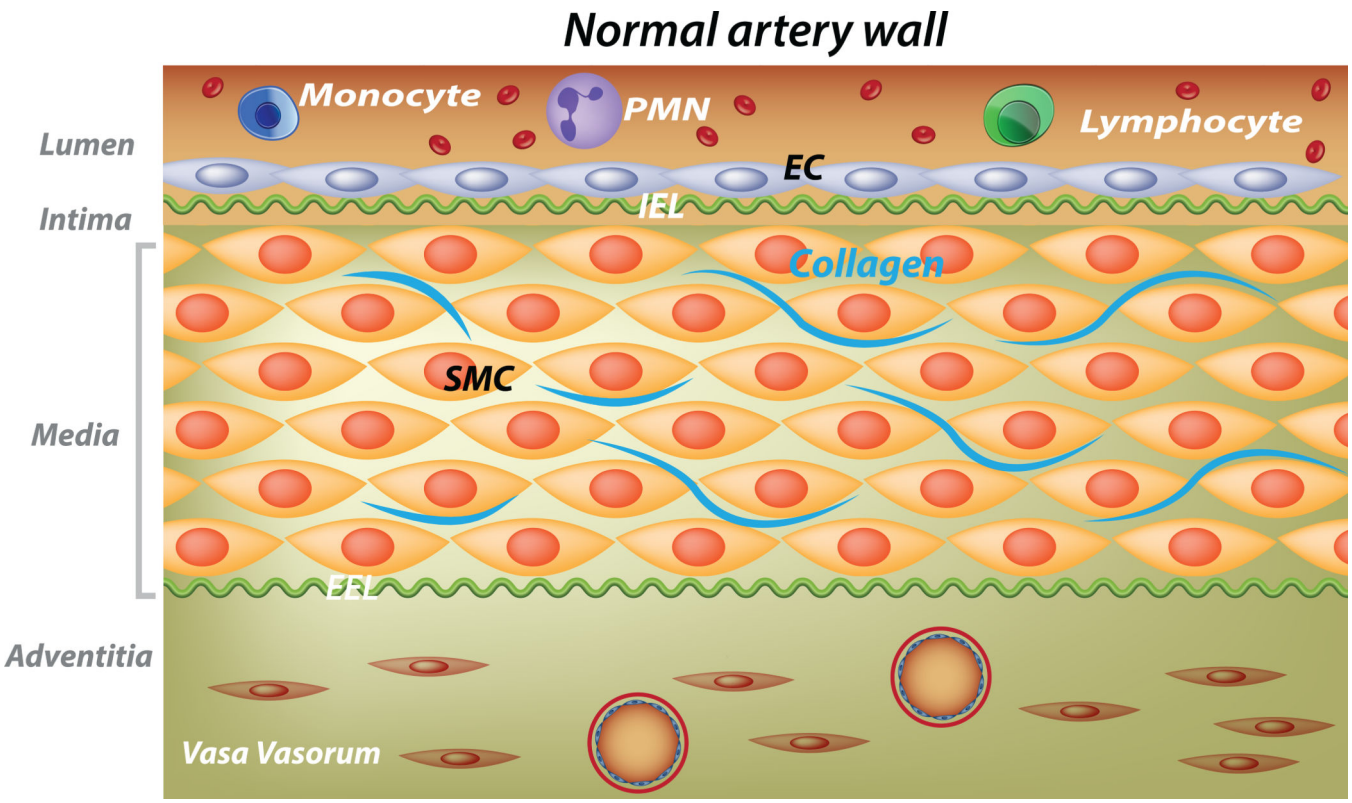

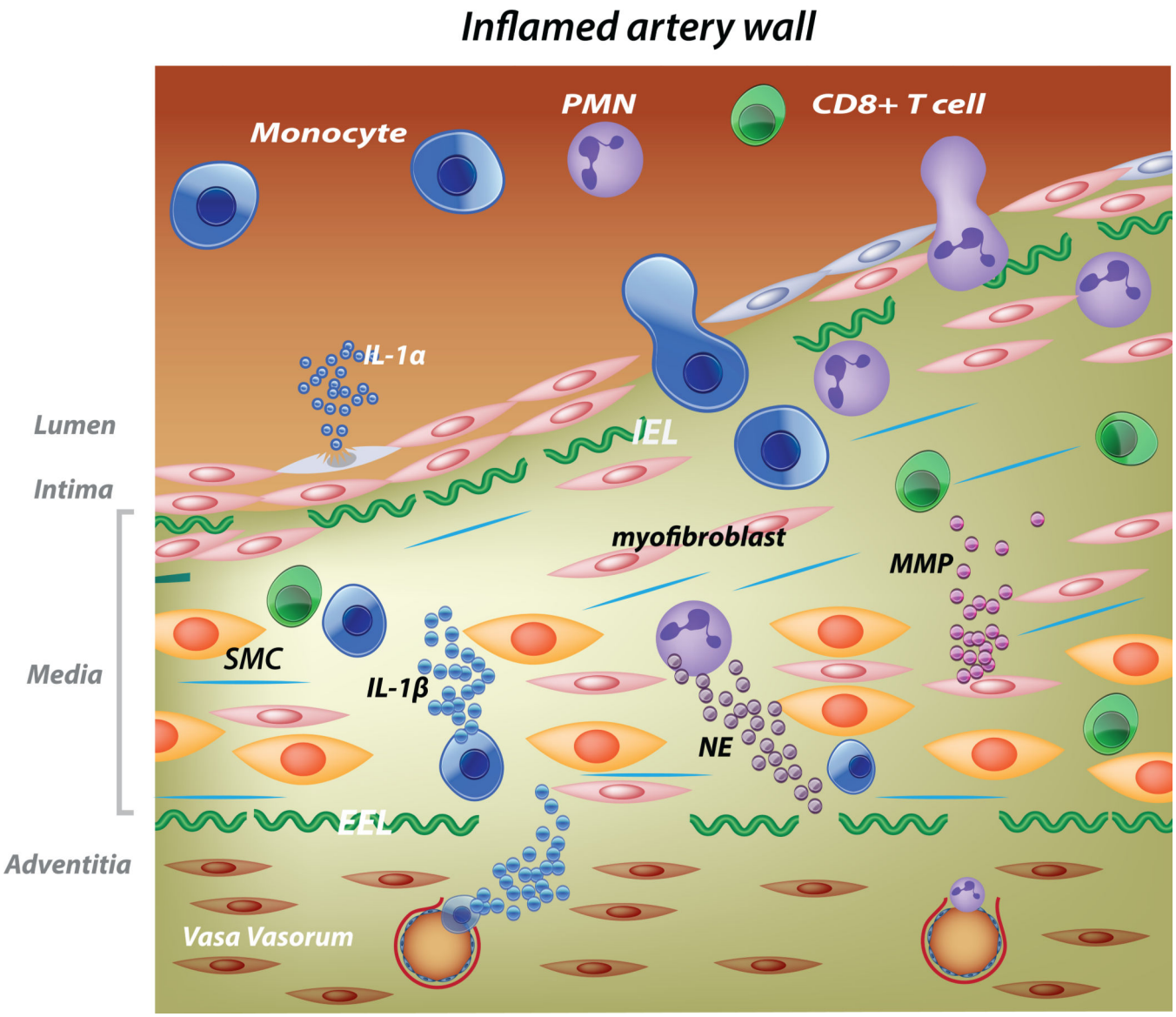

Figure.

Schematic of the vasculitis in acute KD and potential roles of IL-1α and β in disease pathogenesis. In the inflamed artery, endothelial cells (blue spindle-shaped cells) and vascular smooth muscle cells (SMC) transition to myofibroblasts (pink spindle-shaped cells) that secrete matrix metalloproteinases (MMPs) and disordered collagen (blue lines). Neutrophils recruited to the media secrete neutrophil elastases (NE) resulting in breaks in the internal (I) and external (E) elastic lamina (EL). Mononuclear cells trafficking into the media from the lumen and vasa vasorum secrete IL-1β. EC and SMC undergoing necrosis release Il-1α. The structural integrity of the arterial wall is diminished and hydrostatic pressure results in aneurysm formation.

Table 1

Summary of international trials of IL-1 blockade in acute Kawasaki disease subjects.

Name of trial and study medication	Participating centers and country; Target enrollment	Study design	Enrollment criteria	Primary outcome measures	Secondary outcome measures
KAWAKINRA anakinra	6 centers in France, 1 center in Spain, 3 in Italy 20 subjects	Phase II, within subject dose escalation from 2–6 mg/kg/day	IVIG-resistance	Safety, cessation of fever	Coronary artery Z score, changes in gene expression and protein levels of inflammatory biomarkers
ANAKID anakinra	Rady Children's Hospital San Diego and Boston Children's Hospital, USA 30 subjects	Phase I/IIa 3 + 3 dose escalation study from 4–8 mg/kg/day	Z score of RCA and/or LAD ≥ 3.0 and within 20 days of fever onset	Safety, tolerability, PK	Cytokine and oxidative stress measurements, change in Z score of RCA and LAD by echocardiogram
Canakinumab	7 European countries 26 subjects	Phase II 6 mg/kg IV with repeat dose at 4 and 8 weeks	2-arms: treatment-naïve and IVIG resistant	Safety, cessation of fever	Changes in gene expression and protein levels of inflammatory biomarkers