Anakinra And Etanercept Combination Treatment in a Child With Severe, Nonresponsive Kawasaki Disease

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Abstract: Kawasaki disease (KD) patients' resistance to treatment with intravenous immunoglobulins (IVIG) places them at high risk for an unfavorable progression of the disease. In these patients, there has been little evidence that alternative treatments are effective. Nevertheless, biologicals such as an interleukin-1-receptor blocker and tumor-necrosis-factor-α inhibitors increasingly have been used. If the patient does not respond to one of these therapeutics, a combination of 2 biologicals might be an alternative, but this is not yet generally accepted due to the potentially increased risk of infection. Here we report on a 3-month-old boy suffering from severe refractory KD. KD diagnosis was delayed due to the misinterpretation of a urinary tract infection and to the short and nonsimultaneous presence of classical KD symptoms. After complete KD later was able to be diagnosed, treatment with intravenous immunoglobulins was administered. However, the disease proved resistant to 2 courses of IVIG, as well as to corticosteroids. The patient developed giant coronary artery aneurysms early during the course of disease. Anakinra was initiated, but even with stepwise higher anakinra dosages, he remained febrile and coronary artery dimensions increased. Therefore, etanercept was added as a second biological. Only under combination treatment with anakinra and etanercept were his inflammation and fever able to be completely resolved. Coronary artery dimensions improved over time.

Key Words: Kawasaki disease, tumor-necrosis-factor-alpha inhibitor, interleukin-1-receptor antagonist, coronary artery aneurysm

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Kawasaki disease (KD) is an inflammatory, systemic vasculitis that presents during childhood. The classical clinical presentation includes fever, cervical lymphadenopathy, diffuse exanthema, conjunctivitis, oral mucosal changes, and erythema of hands and feet. In terms of morbidity and mortality, the most significant complication is coronary artery aneurysm (CAA)[1,2]. Because the underlying etiologic and pathophysiologic mechanisms remain poorly understood, causal treatment options are lacking. Traditionally, high-dose acetylsalicylic acid (ASS) has been used. Due to its anti-inflammatory effect[1,3], it still is recommended, even though there is no evidence to prove its impact on preventing the development of CAA[4]. Only intravenous immunoglobulin therapy (IVIG) is known to significantly reduce CAA rates[5,6]. IVIG's exact pharmacologic mechanism remains unclear[7]. Although adding corticosteroids to first-line therapy may counteract CAA formation, the medication's efficacy only has been proven in IVIG nonresponsive, high-risk, Japanese KD patients[8,9]. Among pediatric KD patients overall, approximately 10%–20% suffer from IVIG resistance—a resistance associated with a higher risk of developing CAA[1,10]. Although adjunctive therapies for these KD cases have been derived from treatment options for other inflammatory diseases, there is no evidence that they reduce CAA formation in KD.

We report on a severely ill KD patient, resistant to both IVIG and corticosteroid treatment, who developed a giant CAA early during the course of disease. Using anakinra, inflammation improved but did not completely resolve, and CAAs increased further. *After careful consideration, a combination treatment of two biologicals was initiated. To date, such combination treatment has not been documented in the literature for KD patients.* Only with concurrent etanercept treatment was inflammation able to be resolved and coronary artery dimensions decreased over time.

CASE REPORT

A 3-month-old boy presented with high fever (39°C) for 2 days and a diminished general condition. Physical examination at a regional pediatric hospital revealed a pale pink, subtly spotted, coalescent exanthema, which was particularly observable across the upper thorax, palms, and foot soles. He also had redness of the oral cavity, but no palpable lymph nodes were detectable. The mother is a first gravida and primipara. Her vaginal swab was negative for group B streptococcus. Both parents are of Paraguayan descent, but neither had traveled long distance during the previous 15 months.

Laboratory evaluation showed an elevated CRP (11.3 mg/dL), increased gamma-GT (219 U/L), and a mild normocytic anemia (hemoglobin 8.3 g/dL) as shown in Figure 1. Because leukocyturia was detected, the presumptive diagnosis was urosepsis. Urine culture revealed the presence of enterobacter spp. (1×10^3 KBE/mL). The antibiotic treatment regimen was adjusted in response to the antibiogram. Abdominal ultrasound showed hepatomegaly and small bilateral pleural effusions. Due to persistent fever for 7 days without improvement in clinical condition, the patient was transferred to our hospital. Upon admission, the infant was sensitive to touch, had red, chapped lips and palpable, indolent, nuchal lymph nodes. The exanthema, however, had disappeared. CRP continued to be high (14.3 mg/dL). He had leukocytosis (23.0 G/L) and anemia (7.9 g/dL). Platelets were within normal range. Ferritin and liver enzymes were not increased, but hypoalbuminemia (3.0 g/dL) was present. Upon lumbar puncture, liquor pleocytosis (429/µL)

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and elevated protein levels (> 1.000 mg/dL) were detected. Blood cultures and cerebral spinal fluid culture remained sterile. Virologic screening was negative. In addition to the already-known pleural effusions, echocardiography displayed a small, pericardial effusion and normal coronary arteries dimensions. In reviewing the infants' symptoms together with his laboratory and echocardiographic results, we determined there to be sufficient evidence for treating a possible incomplete KD according to AHA guidelines[1]. On day 8 of fever, 1 infusion of IVIG (2 g/kg) and high-dose aspirin (30 mg/kg/d) were initiated. However, the child remained febrile and his clinical condition did not improve within 48 hours following IVIG initiation. After bone marrow puncture excluded a hemato-oncologic disease or hemophagocytosis, a second course of IVIG, together with prednisolone (2 mg/kg/d), was administered. S100A8/A9 (serum calprotectin; 13.673 ng/mL; reference: < 2.940 ng/mL) and serum amyloid A (288 mL/L; Ref.: 6.4 mL/L) were elevated. This indicated immunopathogenesis. Complement factors C3 and C4 were within normal range and uveitis was ruled out. Echocardiography revealed coronary artery ectasia of the right coronary artery (RCA: Z-Score: 2, 3 according to Dallaire and Dahdah[11], day 14). Besides KD, we considered several auto-inflammatory disorders—especially systemic-onset juvenile idiopathic arthritis (sJIA). However, during a more detailed anamnesis with the help of a Spanish language interpreter, the mother mentioned nonsuppurative bilateral conjunctivitis at disease onset. Echocardiographic reexamination showed CAA of the RCA (5 mm; Z-score +11) and left coronary artery (LAD: 4 mm; Z-score +7,6) (day 16). This confirmed our KD diagnosis. After multidisciplinary case discussion and informed consent from both parents, we initiated immunomodulatory therapy with high-dose interleukin-1-receptor-blocker anakinra (6 mg/kg/d, day 16), along with an anticoagulatory therapy (coumadin; target INR of 2–2.5).

After increasing anakinra dosage to 8 mg/kg/d, the patient's fever nearly resolved, but remained subfebrile between 37.5°C

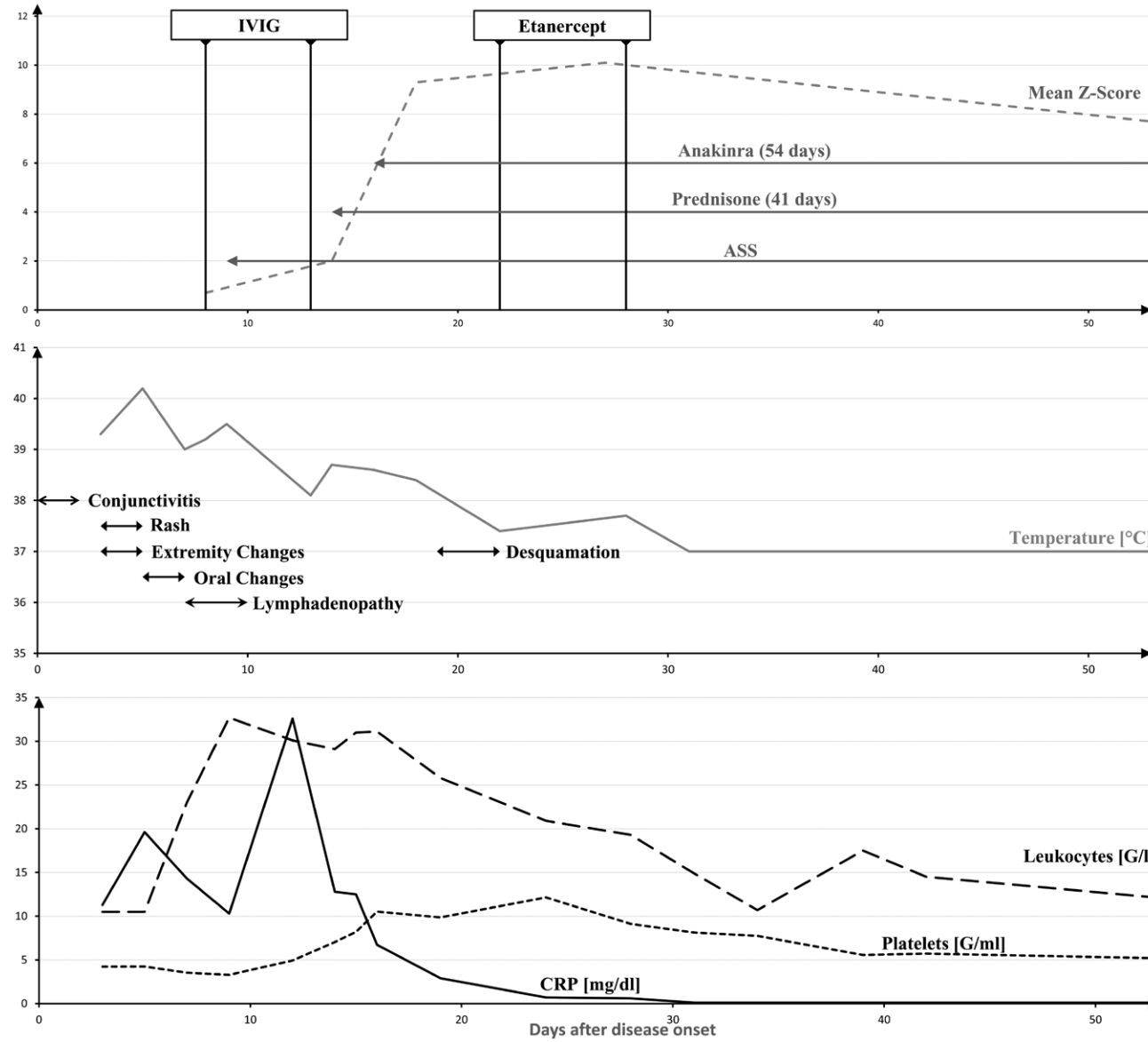

FIGURE 1. Time course of clinical Kawasaki disease (KD) signs and laboratory values in relation to the prescribed KD medications (ASS, prednisone, IVIG, anakinra, etanercept) and days after disease onset.

and 38.0°C. Meanwhile, serum inflammatory markers remained elevated and CAA dimensions increased. Tumor-necrosis-factor-inhibitor etanercept (0.8 mg/kg/wk, day 22) was added as a second biological agent. Following a second dose of etanercept, the infant finally became afebrile and inflammatory markers normalized. Prednisolone and anakinra were phased out over a period of 6 weeks. Coronary artery dimensions decreased over time. Two years later, a cardiac catheter revealed a normal LCA, but a small, distal aneurysm of the RCA (3 × 4 mm) with a less than 50% proximal stenosis remained. Administration of low-dose ASS (3 mg/kg/d) and coumadin was continued.

DISCUSSION

We report on a 3-month-old boy with clinical presentations of severe KD. KD diagnosis was delayed and only later confirmed via the presence of significant coronary artery lesions.

KD rarely is present in infants under 3 months of age. Thus, KD was not considered as a first-line differential diagnosis. However, in our recent, German-wide, population-based study, nearly 5% of children in this age group developed KD and they displayed higher rates of CAA[10]. The misinterpretation of a secondary urine contamination further distracted doctors from an earlier KD diagnosis.

During infancy, children often do not present with a full KD picture. In our patient, all defining clinical KD symptoms were displayed, but they did not all manifest themselves at the same time. We only were made aware of them once a professional language interpreter had been engaged and a closer history-taking was able to be conducted. Although, we initially administered KD-specific therapy following the American Heart Associations' (AHAs) guidelines[12], the AHA's algorithm is not designed to differentiate between different fever etiologies. Even when this child developed coronary artery ectasias (Z-score > 2.0), we still considered other different diagnosis options, particularly systemic-onset juvenile idiopathic arthritis (sJIA)[13]. In sJIA, dilatation of the coronary arteries[14] may be present and serum calprotectin levels are highly elevated—often in the range of > 35,000 ng/mL.[15]

We only can hypothetically speculate about whether the infant would have responded to an earlier therapy initiation or about whether development of CAA could have been prevented. Relatedly, it is unclear whether adding corticosteroids to the first IVIG treatment could have prevented CAA. According to the 2017 AHA guidelines,[1] first-line corticosteroid treatment only remains an option for high-risk patients who cannot reliably be identified among non-Japanese KD patients[16,17]. Nevertheless, according to a recent risk-score model used to investigate North American KD children to predict CAA, this child would have been classified as high risk[18]. Risk variables identified in this investigation, such as young age and highly elevated CRP, also justify a corticosteroid treatment according to the 2018 Italian[19] and 2019 German KD guidelines.

Ultimately, neither IVIG nor corticosteroids significantly influenced the disease course in our patient. Therefore, we proposed first administering the human interleukin-1-receptor blocker anakinra and then later adding the tumor-necrosis-factor-α inhibitor. Inflammation in KD seems to be associated with both signaling pathways.[1] However, there is little evidence for targeting the 2 pathways for treatment of KD. None of these drugs has been approved for KD treatment in Germany, and especially not in such a young child. These drugs only were used in the context of compassionate use after an interdisciplinary case discussion had taken place and informed consent was provide by both parents. Regarding anakinra, 2 multicenter trials (KAWAKINRA and ANAKID) are ongoing. Their results have not yet been reported. Several case reports of IVIG-resistant KD have shown the anakinra therapy to be safe and effective for rapid reduction of inflammation and coronary artery dilatation[20–22]. Therefore, we favored anakinra over the use of other biologicals. We noticed some clinical improvement in our patient, but inflammation persisted—a situation that partially may be explained by the delay in initiating treatment. Because the drug was given 16 days after fever onset, we cannot rule out that this may be related to its limited efficacy. In a case series with eleven patients, however, on average it took almost 25 days after anakinra was administered for clinical improvement to occur[23]. Due to increasing coronary artery dimensions, we decided to add etanercept. In this off-label situation, we preferred etanercept to infliximab due to etanercept's shorter half-life and its lower risk of secondary infections. In a recent multicenter, randomized, double-blind trial, etanercept added to first IVIG treatment did not significantly reduce IVIG resistance. According to a subgroup analysis, however, African American KD patients displayed a small benefit vis-à-vis CAA development[24].

In our case, complete elimination of inflammation occurred only with the application of both biologics—anakinra and etanercept—along with prednisone. At the start, we did not know what the natural course of the disease in this infant would be or how he would respond to anakinra treatment only. Nevertheless, we opted to accept the potentially increased risk of secondary infection, (as is known to exist in patients with rheumatoid arthritis[25]), with the hope that a quick reduction in inflammation would result and therefore positively impact the coronary artery lesions. Our case shows that the burden of disease in giant CAAs—specifically, the high risk of coronary artery ischemia—may justify the use of potentially more harmful therapies in patients with complicated KD. Nevertheless, treatment options in these cases cannot be generalized, but rather should be decided upon on a case-to-case basis by a multidisciplinary team.

CONCLUSION

This case report describes a young infant with severe clinical presentation of KD, resistant to both IVIG and corticosteroids. Although treatment options in this clinical situation are not supported by evidence, both biologicals—interleukin-1 receptor antagonist and TNFα-blockers—increasingly are applied. In severe treatment-resistant cases, the use of a single biological agent may not be effective. After a careful balancing of potential risks, it may be useful to consider combining an interleukin-1-receptor blocker with a tumor-necrosis-factor-α inhibitor.

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