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A Prospective Open-Label Trial of Etanercept as Adjunctive Therapy for Kawasaki Disease

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Abstract

Objective—To determine the safety and pharmacokinetics of etanercept (etanercept, Amgen inc. Thousand Oaks, CA) a tumor necrosis factor- α (TNF- α) receptor blocker, in children with acute Kawasaki disease (KD). Standard therapy of acute KD includes IVIG and high dose aspirin, but a substantial number of patients are refractory and require additional treatment. TNF- α is elevated in children with KD suggesting a role for etanercept in treatment.

Study design—We performed a prospective open label trial of etanercept in patients with KD (6 months to 5 years, $n = 17$) meeting clinical criteria and with fever ≤ 10 days. All received IVIG and ASA. They received etanercept immediately after IVIG infusion and then weekly times two. For initial safety evaluation, the first five patients received 0.4 mg/kg/dose. Subsequent subjects received 0.8 mg/kg/dose.

Results—Fifteen patients completed the study. Pharmacokinetics were similar to older children in published series. No serious adverse events related to etanercept occurred. No patient demonstrated prolonged or recrudescence fever requiring retreatment with IVIG. No patient showed an increase in coronary artery diameter, new coronary artery dilation /cardiac dysfunction.

Conclusion—Etanercept appears to be safe and well tolerated in children with KD. The data support performance of a placebo-controlled trial.

Keywords

Kawasaki's disease; IVIG; TNF- α antagonist; Etanercept; Coronary artery aneurysm

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Kawasaki disease (KD) is the most common cause of acquired heart disease in children in the United States (1). The American Academy of Pediatrics (AAP) and the American Heart Association (AHA) currently recommend high dose aspirin (ASA) and intravenous immunoglobulin (IVIG) for the treatment of acute KD (1). Failure to respond to standard therapy is defined as persistence or recrudescence of fever ($T > 38^{\circ}\text{C}$) 36 hours after completion of IVIG. The failure rate in the U.S. has been reported near 15% in multiple series. However, recent data suggest increasing IVIG resistance and some geographic variation with West Coast centers reporting somewhat higher rates (3) (4). Patients who fail to respond show a six to seven-fold greater risk of coronary artery aneurysm formation compared with responders (5).

Multiple lines of scientific evidence support a particularly prominent role for TNF- α in mediating inflammation in acute and refractory KD. TNF- α signaling triggers enzymatic cleavage and release of soluble TNF- α receptor (6). Patients with KD demonstrate marked elevations in this receptor with the highest levels occurring in patients who, despite receiving IVIG, develop coronary artery ectasia (7).

TNF- α antagonism with the chimeric monoclonal antibodies to TNF (Infliximab) has emerged recently as rescue therapy for patients with refractory KD, even though no large scale clinical trial has been completed to evaluate efficacy (8). Etanercept is FDA approved for children older than 2 years with juvenile idiopathic arthritis, and has been shown to significantly reduce disease severity in children and adolescents with moderate to severe plaque psoriasis (10). However, limited information is available regarding the use of etanercept in children 5 years and younger (11). The acute inflammatory state in patients with KD, as well as elevated levels of immunoglobulin, could alter the safety and pharmacokinetic profile of the drug. TNF- α antagonism could also interfere or modify the therapeutic response to standard KD treatment. Therefore we conducted a pilot clinical trial to obtain data on the safety and pharmacokinetics of etanercept in the initial treatment of children with acute KD. These data established a basis for performance of a larger randomized placebo controlled clinical trial (NCT00841789).

METHODS

We performed an open label non-randomized study evaluating primarily the safety and the pharmacokinetics of etanercept in patients aged 6 months to 5 years. Secondary outcomes were defined as treatment failure (persistence or recrudescence fever 36 hours after completion of IVIG), development of new coronary artery changes at days 14 and 44 after IVIG administration, or development of cardiac dysfunction defined by decreased fractional shortening. Patients were approached if their physicians (independent of the investigation team) intended to treat them with IVIG and aspirin for KD. They were included if they fulfilled the age criteria (6 month-5 years), had fever for 10 days or less, met 4 of the 5 standard clinical criteria for KD or met 3 of 5 criteria with at least 1 dilated coronary artery (internal diameter ≥ 2.5 standard deviations from the mean normalized for body surface area (BSA) [z-score] as determined by echocardiography. Patients were excluded if they had a serious infection, had a history of or recent exposure to tuberculosis, received live vaccine ≤ 6 months prior to enrollment, were exposed to steroids or other immunomodulators, or if they were not treated according to the 2004 AHA/AAP guidelines. The study was approved by the IRB at the Seattle Children's Hospital. Written consent was obtained from the legal guardian. Each subject received an initial IVIG infusion (2 g/kg) and ASA orally at 80 to 100 mg/kg/day in 4 doses until they were afebrile for 24 to 48 hours (according to institutional guidelines) and then the ASA dose was reduced to 3 - 5 mg/kg/day. Three doses of etanercept (Amgen inc. Thousand Oaks CA) (0.8 mg/kg/dose) were administered subcutaneously. The first dose was given within 24 hours of completing IVIG which was defined as day 0. Subsequent doses were administered at day 7 and day 14. For pharmacokinetic analyses, the first 5 patients received 0.4mg/kg/dose.

Adverse events were classified according to severity and possible association with KD or study treatment.

Etanercept serum levels were drawn prior to the administration of each dose and within 48 hours of the administration of the first dose. Samples were submitted to Amgen for the determination of serum drug concentrations. Peak and trough analyses were performed.

Given the limited number of blood samples per patient as required by the institutional review board (IRB) and the number of subjects accrued for the study, a formal pharmacokinetic analysis of etanercept (i.e., area under the curve and plasma clearance) was not feasible. Instead, the plasma concentration-time data in the present group of patients with KD were compared with predictions or simulations in typical older children (>4 years of age) with juvenile idiopathic arthritis (JIA) when placed on the same etanercept regimen used in this study. The simulations were based upon population pharmacokinetic data collected in earlier studies in children with rheumatoid arthritis (Appendix; available at www.jpeds.com). The therapeutic range in the earlier studies on JIA was determined to be 1-4 mg/l (11).

Laboratory assessments, performed at day 0, 48 hours, day 7, day 14 and day 44, included complete blood count (CBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), alanine aminotransferase (ALT), and aspartate aminotransferase (AST). CRP $\leq$ 0.08 mg/dl was assigned for values below the limit of detection.

Echocardiograms were performed at baseline (within 24 hours of study entry) and at day 7 and day 44 after drug administration. In order to maintain consistency with other U.S. clinical trials in KD, the internal lumen diameters of left main coronary artery (LMCA), left anterior descending (LAD), and right coronary artery (RCA) were normalized for BSA as z scores (standard deviation units from a predicted normal mean): dilated ($z \geq 2.5$)(12). Presence of coronary artery aneurysms was determined using the Japanese Ministry of Health Criteria: aneurysm diameter $\geq$ 1.5 times the diameter of the vessel immediately proximal. Left ventricular (LV) systolic function was assessed using LV shortening fraction.

Data are summarized with standard descriptive statistics, including means, standard deviations and selected percentiles. Box plots are used to display the distribution of the coronary artery z-scores and shortening fraction data at each study time point. Changes in these measures from baseline to Week 2 and from baseline to Week 6 were also computed and summarized using means and 95% confidence intervals. Pharmacokinetic analyses are described in the Appendix.

RESULTS

Forty –four patients were screened and twenty-five were deemed eligible for the study. Most were ineligible because they did not demonstrate enough clinical criteria to make the diagnosis of complete KD or they did not fit in the protocol age range. Parents refused participation for eight patients and the remaining seventeen were enrolled between May 2007 and March 2009 at Seattle Children's Hospital. The patients ranged in age from 9 month to 4.8 years with a mean of 2.6 years (± 1.4). The mean weight was 14.6 kg (± 6.2). The first five patients received etanercept at 0.4 mg/kg dose. Patients 6-17 received 0.8 mg/kg/dose. There were 7 females and 8 males. Six patients were younger than 2 years. Racial demographic are represented in Table I. Two patients did not complete the study. A 2 year old male patient met the criteria for protocol eligibility: nine days of high grade fever associated with irritability, swelling and peeling of his lips, strawberry tongue, unilateral cervical lymphadenopathy, history of bilateral nonexudative conjunctivitis, and an erythematous non-purpuric rash in the perineal and diaper area. Laboratory values supported the KD diagnosis: CRP 36 mg/dl hemoglobin (10.1 g/dl), albumin (2.7 g/dl) and platelets ($673 \times 10^3/\text{mm}^3$). A blood culture showed no growth at 48 hours when receiving etanercept, and at final reading. His echocardiogram showed a lack of the

normal tapering of the LAD (proximal and distal LAD 2.0 mm) and perivascular thickening but coronary z-scores were within normal range. The primary medical team made the diagnosis of KD and provided standard treatment with IVIG and ASA. He was enrolled and received one dose of etanercept. He continued to have spiking fevers and a second dose of IVIG was initiated after 36 hours of completion of the initial infusion. His mental status subsequently declined and CSF evaluation revealed meningococcal meningitis. The independent data monitoring committee reviewed the case and determined that the meningitis likely preceded treatment and was not related to the study drug. The event was recognized as a diagnostic error. The second patient was given a second dose of IVIG without knowledge of the study investigators only 12 hours after the completing the first dose for a single fever spike. This was considered a deviation from the protocol and current clinical care guidelines, which recommend no second dose until 36 hours after completion of the IVIG infusion (1).

Other than the single serious adverse event noted above and deemed unrelated to study drug, only mild adverse events occurred (Table II). Local injection reaction, the most common side effect from chronic etanercept administration in children (13), did not occur in this cohort. Etanercept did not appear to adversely affect the treatment response to IVIG. No study patient showed persistence or recrudescence of fever requiring a second dose of IVIG according to AHA/AAP guidelines. CRP values normalized (<0.08 mg/dl) by the first follow up visit on day 7. Platelet count values peaked on day 14 ($452.2 \times 10^3 \pm 183.9$) and decreased to ($360.0 \times 10^3 \pm 75.0$) by day 44. AST and ALT normalized in all patients by day 44. Echocardiographic data is reported for safety due to concerns regarding the potential cardiotoxicity of TNF- α antagonists. No patient showed abnormal cardiac function as assessed by shortening fraction before or after etanercept. There was no significant difference in the shortening fraction on 2 and 6 week echo (Figure 1). The mean change in an individual's shortening fraction from baseline to week 6 was +1.43, with a 95% confidence interval of (-1.62, +4.47). No new coronary artery aneurysms or dilatation developed during the study time period. Summation of maximal coronary artery z-scores are shown in Figure 2. The mean change in an individual's maximal z-score from baseline to week 6 was -0.67, with a 95% confidence interval (-1.20, -0.14). Five patients had coronary artery lesions at baseline (RCA, LAD, LMCA z-score ≥ 2.5). All those patients received etanercept at a dose of 0.8 mg/kg. Three of the five patients had decreases in their maximal coronary artery z-score on their 2 and 6 week echo. One patient had a coronary aneurysm in the RCA (z-score 7.4) and a dilated LAD (z-score 3.5) on the baseline echocardiogram. The coronary aneurysm persisted throughout the study period, but resolved completely as documented on a cardiac catheterization performed 6 month after the initial diagnosis.

Shortening fraction and maximal coronary artery z-score data conform to data noted by McCrindle and others for a large KD population involved in a clinical trial (12).

Peak serum concentrations of etanercept were achieved within the first 48 hours and near steady state levels were achieved by week 2. The mean ($\pm$ SD) peak serum concentration was 3.0 mg/l (± 1.3) and 0.9 mg/l (± 0.5) in patients who received 0.8 mg/kg/dose and 0.4 mg/kg/dose respectively. The drug serum concentrations of both dosing groups are represented in Figures 3 and 4. The trough levels for all patients with KD were similar to simulations from the JIA cohort. Only two of the five patients who received etanercept at 0.4 mg/kg/dose were able to maintain serum levels within the therapeutic range defined by the earlier JIA studies at 1-4 mg/l. However all patients receiving 0.8 mg/kg/dose achieved and maintained serum levels above 1 mg/l except for one patient who received the second dose late. Those less than 2 years showed peak levels between the mean and the 95th percentile for the JIA cohort. The mean apparent $\frac{1}{2}$ life for our study population was 142.3 hours (± 87.4).

DISCUSSION

We assessed the use of a TNF- α antagonist in the initial treatment of KD. Although the majority of patients with KD are effectively treated with the current recommended regimen, a substantial number of patients are left with important coronary vascular lesions. The natural history of coronary lesions remains undefined, particularly in North American populations which display higher risk of coronary atherosclerosis than that of the Japanese cohorts (14). An NIH funded Pediatric Heart Network controlled randomized clinical trial to test the efficacy of pulse methyl-prednisolone as adjunctive therapy prior to standard treatment with IVIG and aspirin failed to show superior therapeutic effect in patients receiving the steroid pulse (15). Thus, broad-based immunomodulation other than through IVIG does not appear effective in U.S. populations with KD. This suggests that a new treatment paradigm is required. Except for adjustments in IVIG dosing, no new therapy has evolved for acute KD in over 23 years.

Despite widespread use of IVIG, the mechanism of action in KD still requires clarification. IVIG reduces TNF- α production in cultured splenocytes exposed to L.Casei wall extract, which promotes Kawasaki type coronary artery disease when injected intraperitoneally in mice(16). Coronary artery damage is absent in wild type mice treated with a TNF- α receptor blocker or deficient for the TNF- α receptor (17). TNF- α promotes accumulation of matrix metalloproteinase 9 (MMP9), which is involved in coronary artery elastin breakdown in the mouse model (18). Salicylates, at presumed therapeutic concentrations as used in the initial treatment of acute KD, prevent the inhibitory action of IVIG on TNF- α in cell culture (16). Some have suggested that these data *in vitro* and in the mouse model provide rationale for use of TNF- α blockade as salvage therapy in KD (17). However, the diagnosis of acute KD is made well after initiation of the inflammatory process and production of TNF- α . Furthermore, rescue therapy is provided only to IVIG recalcitrant patients, who likely already have developing coronary artery vasculitis. We proposed a treatment paradigm for all patients with acute KD, which would adequately suppress TNF- α action unlike the current regimen.

Several ethical burdens hinder the performance of pharmacokinetic studies in young infants and children. These include fear and pain associated with multiple blood draws which are not related to clinical care. Accordingly, the pharmacokinetic profile in adults is often extrapolated to children. Yim and coauthors evaluated the pharmacokinetic profile of etanercept in children with JIA (11) who were for the most part older than our KD cohort, and provided a more reasonable population for comparison than adults. However, differences in the inflammatory state between these two diseases, as well as possible effects of IVIG on drug distribution and metabolism could influence the pharmacokinetics in children with KD and yield discrepancies with the JIA population. Thus, reasonable estimate of pharmacokinetics in the specific KD population was necessary before proceeding to a larger clinical trial. The pharmacokinetic profile of etanercept, obtained from our population, is similar to those determined from older JIA cohorts receiving weekly dosing at 0.8 mg/kg SC (11). Trough levels for patients across the age group in our study were near the lower limit of therapeutic range, showing that this cohort showed expected drug clearance. Peak levels appear slightly higher in the patients with KD less than 2 years of age. The higher peak concentration could be explained by either more rapid, complete SC absorption or smaller volume of distribution (per kg body weight).

In order to maintain therapeutic levels throughout the KD course, treatment was extended 2 weeks after initial IVIG treatment. Coronary artery involvement can occur late in the acute phase. Furthermore refractoriness to IVIG can manifest up to 2 weeks after completion of IVIG thereby providing rationale for our treatment duration (19). The observed pharmacokinetics allow the termination and reasonable clearance of etanercept if necessitated by a drug related adverse event or intercurrent infection. This contrasts to infliximab which remains at therapeutic doses or higher for extended time periods in Kawasaki patients (20). The SC route

also yields less severe fluctuations in the serum peak and trough concentrations than observed with intravenously administered TNF- α antagonists (21,22).

There was one serious adverse event reported in our trial. Some of the illness manifestations were retrospectively attributed to meningococcal infection in that particular patient, although this patient fit protocol criteria, and had negative blood cultures. Although it was deemed by regulatory bodies as unrelated to the study drug, this event highlights that human error is a potential hazard of giving an immunomodulating drug for a febrile illness without a diagnostic test. Lack of a specific biomarker remains an important diagnostic problem in KD and other diseases. In particular, meningococcal disease can closely resemble KD. For instance, there are isolated reports of meningococcal sepsis preceding a Kawasaki like illness with coronary artery involvement (23,24). Etanercept could have exacerbated or facilitated the infection in this particular patient as case reports exist for listeria and pneumococcal meningitis in patients on etanercept(25,26). However, the patients described in those reports received etanercept and other immunosuppressant drugs for more than 10 months prior to the diagnosis of the bacterial meningitis. Our patient received only a single dose of etanercept making a role for participation in the meningococcal infection unlikely. The remaining adverse events were minor, self-limited, and consistent with the etanercept safety profile noted in other studies in children (13). The lack of injection site reactions in our cohort suggests that this hypersensitivity reaction occurs only after prolonged therapy.

Treatment with TNF- α antagonists in the patients with KD does raise some safety concerns due to the potential for myocarditis and developing coronary artery abnormalities and ischemia. Furthermore, differences exist among TNF- α antagonists regarding safety. Short-term TNF- α antagonism with infliximab did not improve and high doses (10 mg/kg) adversely affected the clinical condition of adult patients with moderate-to-severe chronic heart failure (27). The mechanism for worsening heart failure with monoclonal antibodies is thought to be the direct binding of TNF- α antagonists to the transmembrane form of TNF- α receptor resulting in damage to TNF- α expressing cells including cardiomyocytes (28). Etanercept shows low binding affinity to the transmembrane form of TNF- α , and is less active in mediating cytotoxicity (29). This difference from the chimeric monoclonal antibodies might explain why etanercept has not been implicated in worsening of heart failure. Two etanercept trials in adults with chronic heart failure were terminated due to lack of efficacy, not because of an increase in mortality or adverse events (30,31). As this was a nonrandomized observational pilot study, we could not perform a statistical analysis to evaluate cardiac safety. However, no patient in our study showed a new coronary artery abnormality, progressive coronary dilation, or systolic cardiac dysfunction while on etanercept.

The FDA has recently issued a black box warning regarding the risk of TB and cancer (mainly lymphomas) in patients receiving etanercept. Reactivation of chronic granulomatous disease including tuberculosis (TB) from the chronic treatment with TNF- α antagonist is a valid safety concern. However, a recent review by Manadan et al showed that none of the 48 patients with positive PPDs who were treated with etanercept for an average of 17 months developed active TB (32). The use of additional immunosuppression was found to be a risk factor for TB. The risk of developing or reactivating TB in our cohort is markedly reduced because etanercept was administered over a short period of time (2 weeks) with no concomitant exposure to immunosuppressive drugs. The risk of TB or latent TB reactivation in patients receiving etanercept might be higher in areas endemic for TB. Despite data from studies of adults with RA indicating a possible association between anti-TNF use and lymphomas, the existence of a cause and effect relationship remains controversial (33). There were no cases of malignancies, TB, or opportunistic infections noted in patients with JIA who received chronic etanercept treatment when followed for up to 8 years (34).

The design of this pharmacokinetic and observational safety study does not permit the assessment of efficacy of etanercept in the treatment of KD. The data obtained do support the performance of larger efficacy trials for etanercept in pediatric patients with KD.

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ABBREVIATIONS

AAP	American Academy of Pediatrics
AHA	American Heart Association
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
BSA	Body Surface Area
CBC	complete blood count
CRP	C- reactive protein
CSF	Cerebral spinal fluid
ESR	Erythrocyte sedimentation rate
IVIG	Intravenous immunoglobulin G
IRB	Institutional review board
JIA	Juvenile idiopathic arthritis
KD	Kawasaki disease
LAD	Left anterior descending
LMCA	Left main coronary artery
RCA	Right coronary artery
RA	Rheumatoid arthritis
TNF-α	Tumor necrosis factor α
URIs	Upper respiratory tract infections

Figure 1. Left ventricular shortening fraction (median and quartile, $n = 15$). All patients had a normal SF at baseline. There was no significant change in the SF over the study time period.

Figure 2. Maximal coronary artery z score median and quartile data for all patients (n = 15). No new coronary artery dilation/aneurysms developed during the study time period. The individual dots represent the patient who had a RCA aneurysm and a dilated LAD.

Figure 3.

Etanercept serum concentrations over time for 0.4mg/kg dosing. Each symbol represents a single patient with KD. The dotted and dashed lines are superimposed simulations of the mean from the JIA cohort females and males respectively. The solid lines represent the 5th and 95th percentiles.

Figure 4.

Etanercept serum concentrations over time for 0.8mg/kg dosing. Each symbol represents a single patient with KD. Open symbols and (+) are patients < 2 years of age. The dotted and dashed lines are superimposed simulations of the mean from the JIA cohort females and males at 0.8mg/kg/dose once weekly. The solid curves represent the 5th and 95th percentile for the JIA cohort.

TABLE 1**Racial Demographics**

Race	n
African American	1
Asian	3
Hispanic	3
White [^]	5
Other [*]	3

[^] White: Caucasian non-Hispanic.

^{*} Other: patients were Caucasian/Asian/Hawaiian, African American/Indian/Hawaiian/Pacific Islander, and Asian Pacific Islander

TABLE 2**Adverse Events**

Adverse Events	n
Serious adverse event	
Meningococemia (unrelated to study drug)	1
Mild adverse events	
Upper respiratory tract infections (URIs) [*]	2
Otitis media	1
Gastrointestinal symptoms /vomiting	1
Photophobia [†]	1
Subconjunctival hemorrhage [†]	1

^{*} URIs were associated with similar symptoms in family members.

[†] Unilateral subconjunctival hemorrhage occurred 24 hours after the first dose of etanercept and photophobia 48 hours after the second dose in the same patient. Both symptoms resolved spontaneously within 12 days and 24 hours respectively.