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Infliximab for intensification of primary therapy for Kawasaki disease: a phase 3 randomised, double-blind, placebo-controlled trial

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Summary

Background Kawasaki disease, the most common cause of acquired heart disease in developed countries, is a self-limited vasculitis that is treated with high doses of intravenous immunoglobulin. Resistance to intravenous immunoglobulin in Kawasaki disease increases the risk of coronary artery aneurysms. We assessed whether the addition of infliximab to standard therapy (intravenous immunoglobulin and aspirin) in acute Kawasaki disease reduces the rate of treatment resistance.

Methods We undertook a phase 3, randomised, double-blind, placebo-controlled trial in two children's hospitals in the USA to assess the addition of infliximab (5 mg per kg) to standard therapy. Eligible participants were children aged 4 weeks–17 years who had a fever (temperature ≥38·0°C) for 3–10 days and met American Heart Association criteria for Kawasaki disease. Participants were randomly allocated in 1:1 ratio to two treatment groups: infliximab 5 mg/kg at 1 mg/mL intravenously over 2 h or placebo (normal saline 5 mL/kg, administered intravenously). Randomisation was based on a randomly permuted block design (block sizes 2 and 4), stratified by age, sex, and centre. Patients, treating physicians and staff, study team members, and echocardiographers were all masked to treament assignment. The primary outcome was the difference between the groups in treatment resistance defined as a temperature of 38·0°C or higher at 36 h to 7 days after completion of the infusion of intravenous immunoglobulin. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, NCT00760435.

Findings 196 patients were enrolled and randomised: 98 to the infliximab group and 98 to placebo. One patient in the placebo group was withdrawn from the study because of hypotension before receiving treatment. Treatment resistance rate did not differ significantly (11 [11·2%] for infliximab and 11 [11·3%] for placebo; p=0·81). Compared with the placebo group, participants given infliximab had fewer days of fever (median 1 day for infliximab *vs* 2 days for placebo; p<0·0001). At week 2, infliximab-treated patients had greater mean reductions in erythrocyte sedimentation rate (p=0·009) and a two-fold greater decrease in *Z* score of the left anterior descending artery (p=0·045) than did those in the placebo group, but this difference was not significant at week 5. Participants in the infliximab group had a greater mean reduction in C-reactive protein concentration (p=0·0003) and in absolute neutrophil count (p=0·024) at 24 h after treatment than did those given placebo, but by week 2 this difference was not significant. At week 5, none of the laboratory values differed significantly compared with baseline. No significant differences were recorded between the two groups at any timepoint in proximal right coronary artery *Z* scores, age-adjusted haemoglobin values, duration of hospital stay, or any other laboratory markers of inflammation measured. No reactions to intravenous immunoglobulin infusion occurred in patients treated with infliximab compared with 13 (13·4%) patients given placebo (p<0·0001). No serious adverse events were directly attributable to infliximab infusion.

Interpretation The addition of infliximab to primary treatment in acute Kawasaki disease did not reduce treatment resistance. However, it was safe and well tolerated and reduced fever duration, some markers of inflammation, left anterior descending coronary artery *Z* score, and intravenous immunoglobulin reaction rates.

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Introduction

Intravenous immunoglobulin treatment of patients with acute Kawasaki disease reduces the occurrence of aneurysms from 25% to 5%. However, around 10–20% of patients with Kawasaki disease develop persistent or recrudescent fever after standard therapy with a single infusion of intravenous immunoglobulin and aspirin.[1,2] This subset of immunoglobulin-resistant patients is at highest risk for developing coronary artery aneurysms, and needs additional treatment to interrupt the inflammatory process. Therefore, intensification of initial therapy to prevent intravenous immunoglobulin-resistance and associated coronary artery abnormalities remains a valid approach to address this unmet clinical need.

Tumour necrosis factor (TNF) α and TNFα soluble receptors I and II concentrations are increased in the acute phase of Kawasaki disease, and are highest in children who subsequently develop coronary artery aneurysms.[3,4] In

See Online for appendix

view of the importance of TNFα in the genesis and maintenance of inflammation,[5] either primary treatment of patients or treatment of highly resistant patients with a TNFα antagonist is a logical therapeutic intervention. An open-label trial of etanercept, a TNFα receptor blocker, in children with Kawasaki disease showed that this drug added to primary treatment was safe and well tolerated.[6] Early experience with infliximab, a chimeric monoclonal antibody that specifically binds TNFα, showed promising results.[7] A phase 1, randomised, multicentre clinical trial in children with Kawasaki disease and persistent or recrudescent fever after standard therapy reported no infusion reactions or serious adverse events attributable to infliximab.[8] In a subsequent two-centre retrospective study of intravenous immunoglobulin-resistant disease, re-treatment with infliximab resulted in faster resolution of fever and fewer days of hospitalisation than did a second intravenous immunoglobulin infusion.[9] These data suggest that infliximab is safe and effective in reducing inflammation in acute Kawasaki disease. Therefore, we postulated that intensification of initial therapy with infliximab would decrease the rate of resistance to intravenous immunoglobulin and prevent adverse coronary artery outcomes.

Methods

Study design and patients

We did a phase 3, randomised, double-blind, placebo-controlled, two-centre trial. From March, 2009, to August, 2012, we recruited patients from Rady Children's Hospital San Diego, CA, USA, and Nationwide Children's Hospital in Columbus, OH, USA. Eligible participants were children aged 4 weeks–17 years with Kawasaki disease who had fever (≥38·0°C) for 3–10 days. The full inclusion criteria, as per the American Heart Association case definitions, and exclusion criteria are listed in the appendix.[10] Because many children with Kawasaki disease are anergic to delayed-type hypersensitivity skin tests, all patients also had a chest radiograph within the week before infusion of study drug with no evidence of tuberculosis or other infection. The study protocol was reviewed and approved by the University of California San Diego's and Nationwide Children's Hospital's Institutional Review Boards. Written informed consent was obtained from the parents or legal guardians and assent, when appropriate, was obtained from the patient.

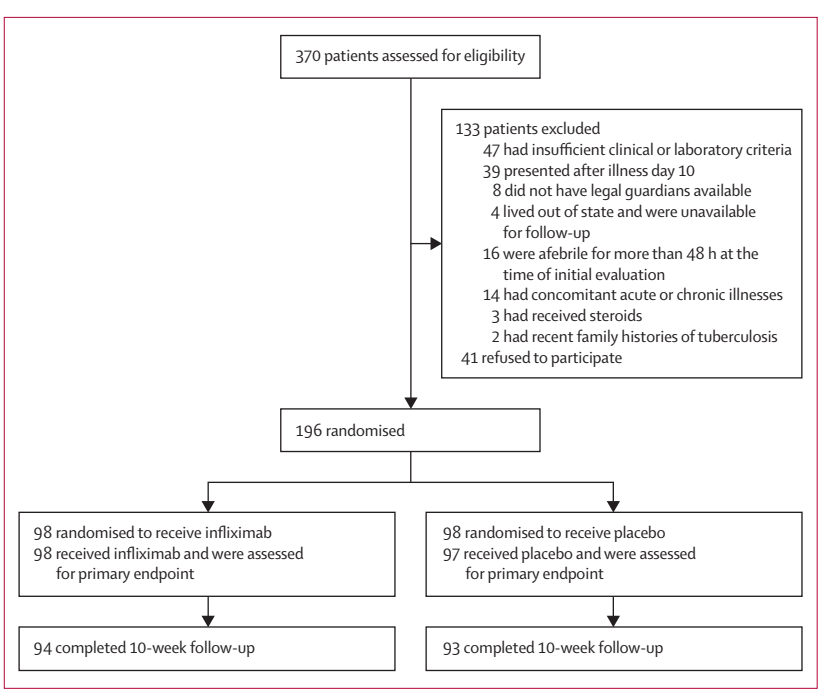

Figure: Trial profile

Randomisation and masking

After validation of eligibility criteria, patients were randomly assigned to either the infliximab or placebo group in a 1:1 ratio. Randomisation was based on a randomly permuted block design with block sizes of two and four participants, stratified by age (<1 year or ≥1 year), sex, and centre. Patients received either infliximab (5 mg/kg at 1 mg/mL intravenously over 2 h) or placebo (normal saline intravenously, 5 mL/kg; figure). Patients, treating physicians and staff, study team members, and the echocardiographer were all masked to assignment. The placebo was similar in colour, volume, and manner of administration to the infliximab.

Procedures

After randomisation, all patients received diphenhydramine (1 mg per kg intravenously, maximum 50 mg) and acetaminophen (15 mg per kg orally, maximum 650 mg) 30 min before receiving study drug. All patients received intravenous immunoglobulin (Gammagard [Baxter Pharmaceuticals, Westlake Village, CA, USA], 2 g per kg over 10–12 h) immediately after administration of study drug. Aspirin (80–100 mg/kg per day divided every 6 h) was administered orally until the patient was discharged from the hospital when the dose was reduced to 3–5 mg/kg per day for the duration of the study, or longer if clinically indicated. The primary outcome measure, treatment resistance, was defined as a temperature of 38·0°C or higher between 36 h and 7 days after completion of the intravenous immunoglobulin infusion without another likely source. Treatment-resistant children received a second infusion of intravenous immunoglobulin (2 g per kg). Patients who had persistent fever 24 h after the end of their second intravenous infusion without another likely source were treated at the discretion of the centre investigator.

After completion of the intravenous immunoglobulin infusion, body temperatures were measured every 6 h before the aspirin dose by either the rectal or oral route with a digital thermometer. On discharge, the legal guardian recorded temperatures by the oral, rectal, or

axillary route once a day for 3 days. The family was contacted by a study coordinator 3 days and 10 weeks after discharge to monitor the child's recovery.

Secondary outcome measures were: Z_{max} (largest of the blinded, single-observer, echocardiographic measurements of the internal diameter normalised for body surface area of the proximal right coronary artery and left anterior descending coronary artery at weeks 2 and 5 after treatment) and change in Z score from baseline to weeks 2 and 5; change in concentrations of age-adjusted haemoglobin, C-reactive protein, alanine transaminase, albumin, and γ-glutamyl transferase; change in erythrocyte sedimentation rate, platelet count, white blood cell count, and absolute cell counts; number of fever days (24 h period with a temperature of at least 38·0°C) from enrolment; duration of hospital stay; and intravenous immunoglobulin and infliximab infusion reactions.[11]

We obtained laboratory data at baseline, 24 h after completion of the intravenous immunoglobulin infusion, and at week 2 (study day 14, or within 2 days beforehand or afterwards; Rady Children's Hospital site only) and week 5 (study day 35, or within 2 days beforehand or afterwards) after randomisation. Echocardiograms were obtained during the initial hospitalisation and at the week 2 and 5 visits. Patients younger than 3 years were sedated with chloral hydrate (75 mg/kg per dose orally, maximum 1 g) for the echocardiogram.[12] An echocardiographer (BFP) interpreted all echocardiograms across both centres and reported coronary artery dimensions as Z scores.[13] Patients were classified as having normal (Z score <2·5), dilated (Z score ≥2·5), or aneurysmal (focal dilation of an arterial segment ≥1·5 times the diameter of the adjacent segment) coronary arteries based on the maximum internal diameters of the proximal right coronary artery or left anterior descending coronary artery.

An intravenous immunoglobulin infusion reaction was defined as fever with chills or hypotension for age that warranted interruption of the intravenous immunoglobulin infusion. A data and safety monitoring board reviewed safety data after enrolment of 25, 50, and 100 patients.

Statistical analyses

To have 80% power to detect a reduction in treatment resistance from 20% to 5%, with a two-sided α of 0·048 and an attrition rate of 10%, based on a two-sample binomial test for proportions, the study required 196 participants. The data and safety monitoring board did an interim analysis for efficacy (with a threshold of 0·002) after 100 participants were enrolled.

The primary outcome was analysed on the basis of a modified intent-to-treat population, which was defined as all the randomised patients who received study drug (98 infliximab and 97 placebo). The primary analysis used a logistic regression model to compare the resistance rates between groups adjusting for illness days (illness day 1=first day of fever), alanine transaminase, γ-glutamyl transferase, age-adjusted haemoglobin, and percent bands at baseline, previously identified as predictors of intravenous immunoglobulin resistance.[2] For the secondary outcome measure of coronary artery internal dimension, a linear regression model was used to compare Z_{max} between treatment groups, adjusted for the same covariates as in the primary analysis. Change in Z scores from baseline for the left main coronary artery and proximal right coronary artery and left anterior descending coronary artery at week 2 and week 5 were analysed with mixed model repeated measures. The timepoint was treated as a categorical variable and an unstructured variance-covariance error matrix was applied. The laboratory values that were secondary outcome measures were assessed at several timepoints. If the parameter was measured at more than two timepoints, similar mixed model analysis as described above was done. If the parameter was measured only at two timepoints, an

	Infliximab (n=98)	Placebo (n=98)
Age (years)	3·0 (1·9–4·8)	2·8 (1·8–4·2)
Age <1 year	11 (11·2%)	9 (9·2%)
Male sex	60 (61·2%)	61 (62·2%)
Race		
White	61 (62·2%)	59 (60·2%)
Asian	10 (10·2%)	14 (14·3%)
African–American	10 (10·2%)	8 (8·2%)
Native Hawaiian or other Pacific islander	1 (1%)	0
More than one race	15 (15·3%)	17 (17·3%)
Unknown	1 (1)	0
Hispanic ethnic origin	57 (58·2%)	64 (65·3%)
Days of illness at enrolment*	6 (5–7)	5 (4–7)
White blood cell count (×10⁹/L)	13·4 (10·3–17·6)	13·1 (11·2–16·8)
zHgb†	−1·4 (−2·4 to −0·5)	−1·4 (−2·3 to −0·5)
Platelet count (×10⁹/L)‡	350 (266–420)	338 (270–433)
C-reactive protein (nmol/L)	790·5 (542·9–1495·3)	838·1 (438·1–1485·7)
Erythrocyte sedimentation rate (mm/h)	57 (44–69)	58 (45–74)
Alanine transaminase (μkat/L)‡	0·8 (0·3–1·9)	1·0 (0·3–2·1)
γ-glutamyl transferase (μkat/L)‡	1·1 (0·4–2·8)	1·2 (0·4–2·8)
Albumin (g/L)‡	36 (33–39)	37 (34–37)
Z scores§		
Proximal left anterior descending coronary artery	1·2 (1·5)	1·3 (1·2)
Proximal right coronary artery	0·9 (1·4)	0·9 (1·2)
Left main coronary artery	0·9 (1·0)	0·8 (1·0)
Aortic annulus	0·5 (0·8)	0·5 (0·9)
Aortic sinus	0·4 (0·8)	0·3 (0·9)

Data are median (IQR), n (%), or mean (SD), unless otherwise indicated. *First day of illness is defined as the first day of fever. †SD units from the mean for age-adjusted haemoglobin values.[11] ‡Laboratory data were available for all 196 participants, except for platelets (n=195), alanine transaminase (n=195), γ-glutamyl transferase (n=192), and albumin (n=194). §Z scores were calculated as previously published;[13] coronary artery measurements were available as follows: left anterior descending coronary artery (n=192), right coronary artery (n=189), left main coronary artery (n=189), aortic annulus (n=193), and aortic sinus (n=193).

Table 1: **Baseline demographics and clinical characteristics of study population by treatment group**

	Infliximab	Placebo	p value
Primary outcome			
Treatment resistance*	11 (11·2%)	11 (11·3%)	0·81
Secondary outcomes			
IVIG infusion reaction	0	13 (13·4%)	<0·0001
Days of hospital stay	3 (3–4); range: 2–7	3 (3–4); range: 1–8	0·65
Days of fever†	1 (1–2); range: 0–4	2 (1–2); range: 0–6	<0·0001

Data are n (%) or median (IQR), unless otherwise indicated. IVIG=intravenous immunoglobulin. *Treatment resistance, the primary outcome, and IVIG infusion reaction were analysed on the basis of a modified intention-to-treat population, which was defined as all the randomised participants who received study drug (infliximab n=98; placebo n=97).†Days of fever=number of calendar days from the day of enrolment with any temperature ≥38°C. Days of hospital stay and days of fever were analysed based on all randomised participants (n=98 per group).

Table 2: **Treatment resistance, IVIG infusion reactions, duration of hospital stay, and days of fever in the study population by treatment group**

	Infliximab (n=96)*	Placebo (n=97)*
Coronary artery classification†		
Normal	70 (72·9%)	70 (72·2%)
Dilated	22 (22·9%)	21 (21·7%)
Aneurysm	3 (3·1%)	5 (5·2%)
Giant aneurysm	1 (1%)	1 (1%)
Proximal left anterior descending artery *Z* score		
Baseline	1·2 (1·5)	1·3 (1·2)
Week 2	0·7 (1·1)	0·9 (1·4)
Week 5	0·5 (1·2)	0·8 (1·6)
Proximal right coronary artery *Z* score		
Baseline	0·9 (1·4)	0·9 (1·2)
Week 2	0·6 (1·5)	0·7 (1·3)
Week 5	0·3 (1·4)	0·6 (1·8)

Data are n (%) or mean (SD). *n=96 (infliximab group) and n=97 (placebo group) because maximum internal diameters of the left anterior descending and right coronary arteries not well visualised on echocardiogram in a few participants. †Participants were classified as having normal (*Z* score <2·5), dilated (*Z* score ≥2·5), or aneurysmal (focal dilation of an arterial segment ≥1·5 times the diameter of the adjacent segment) coronary arteries based on the maximum internal diameters of the proximal right coronary artery or left anterior descending artery.

Table 3: **Coronary artery classification and *Z* scores for the study population by treatment group**

ANCOVA model was used to assess the difference between the treatment groups in change score, with adjustment for the baseline measure. Intravenous immunoglobulin infusion reaction rates were compared between groups with Fisher's exact test. Duration of hospital stay and number of fever days were analysed with the Wilcoxon rank sum test. Safety data were summarised by treatment groups and overall. Fisher's exact test was used to compare the number of patients who experienced any adverse events between the groups. A p value of less than 0·05 was considered statistically significant for secondary measures. No adjustments were made for multiple comparisons. Statistical analyses were done in R, version 2·14·0.

This study is registered with ClinicalTrials.gov, number NCT00760435.

Role of the funding source

Grant support was provided by the US Food and Drug Administration and the Robert Wood Johnson Foundation. Janssen Biotech, the manufacturer of infliximab, provided commercial-grade drug for this study. The sponsors of this study had no role in the study design, data collection and analysis, or decision to submit for publication. Janssen Biotech reviewed the manuscript and suggested changes, but the final decision on content was retained exclusively by the authors.

Results

Of the 370 children treated for Kawasaki disease at both sites during the study period, 133 (36%) did not qualify because they failed to meet strict eligibility criteria (n=86) or had one or more exclusion criteria (n=47; figure). Of the 237 study-eligible patients, the parents of 196 (83%) gave written consent, and these patients were randomly assigned to either the infliximab or placebo group (n=98 in each group). Of the 196 patients enrolled, 183 (93%) had at least four clinical criteria for Kawasaki disease, whereas 12 (6%) and one (0·5%) qualified with two or more clinical criteria plus supporting laboratory values or an abnormal echocardiogram, respectively.

One patient in the placebo group was withdrawn from the study because of hypotension before receiving the study drug and was considered too ill by the study investigators to participate. All 196 patients were successfully contacted by telephone and reported no adverse events since the last study visit. 132 of the 196 patients have returned for a 1-year follow-up assessment by one of the investigators and none have reported a serious illness since completion of the study.

Baseline characteristics were similar between the two groups (table 1). The primary endpoint, treatment resistance, was similar in both groups, irrespective of site, with 11 (11·3%) of 97 patients in the placebo group and 11 (11·2%) of 98 in the infliximab group resistant to treatment (table 2). Four of the re-treated patients (two in the placebo and two in the infliximab group) were given a second intravenous immunoglobulin infusion before the 36 h timepoint specified in the protocol because of the clinical severity of their illness. A logistic regression model, with adjustment for illness day at enrolment and baseline alanine transaminase, γ-glutamyl transferase, percent bands, and age-adjusted haemoglobin, showed no difference in the treatment resistance rates between study groups (p=0·81). The median days of fever in the infliximab group was 1 (range 0–4) compared with 2 days (range 0–6) in the placebo group (p<0·0001; table 2). No patients receiving infliximab had intravenous immunoglobulin infusion reactions, compared with 13 (13·4%) of those receiving placebo (p<0·0001).

Table 3 shows the coronary artery *Z* scores and classification for the study population by treatment group. Compared with baseline, there was a two-fold

greater decrease in the mean *Z* score of the proximal left anterior descending coronary artery in the infliximab group compared with placebo at week 2 (p=0·045; table 4, appendix), but no significant difference at week 5. There were no differences in the left main coronary artery or proximal right coronary artery *Z* scores compared with baseline at week 2 and week 5, or in the Z_{max} between treatment groups (table 4). A post-hoc analysis of the mean change from baseline of the left main coronary artery and proximal right coronary artery *Z* scores of the 45 patients (25 in infliximab group, 20 in placebo group) with a baseline *Z* score of 2·5 or higher showed no difference between treatment groups.

The reduction in the concentration of C-reactive protein and absolute neutrophil count from baseline to 24 h after completion of intravenous immunoglobulin was greater in patients in the infliximab group than in the placebo group (p=0·0003 for C-reactive protein and p=0·024 for absolute neutrophil count) but similar at week 2 (table 5). There was also a greater reduction in erythrocyte sedimentation rate at week 2 compared with baseline in the infliximab group than in the placebo group (p=0·009). There were no statistically significant differences at week 5 compared with baseline for any of the laboratory values.

The adverse events are summarised by group in table 6. The number of patients who had one or more adverse events did not differ significantly between the groups (56 [57·1%] infliximab *vs* 66 [67·4%] placebo, p=0·18). No serious adverse event was related to the study drug.

Discussion

The addition of infliximab to initial therapy did not affect treatment resistance. However, administration of infliximab shortened the duration of fever, eliminated the risk of infusion reactions if given before intravenous immunoglobulin, and more rapidly reduced inflammation as evidenced by greater reductions in the concentration of C-reactive protein and absolute neutrophil count at 24 h and in erythrocyte sedimentation rate at week 2. We also showed that patients who received infliximab had a larger decrease in the *Z* score of the left anterior descending coronary artery at week 2 than at baseline, suggesting that the primary outcome of a larger multicentre trial of infliximab should perhaps be adverse coronary artery outcomes.

Intensification of initial treatment in Kawasaki disease has been studied in six randomised clinical trials in which corticosteroids were added to standard intravenous immunoglobulin plus aspirin to prevent coronary artery sequelae (panel).[14–19] A meta-analysis of these studies concluded that the addition of corticosteroids to intravenous immunoglobulin resulted in fewer coronary artery abnormalities than with treatment with intravenous immunoglobulin alone (OR 0·3, 95% CI 0·18–0·5).[20] However, heterogeneity in patient selection and treatment protocols severely limits application to our patient population. Three studies assessed 3–5 days of intravenous methylprednisolone (2 mg/kg per day) followed by a 2–4 week oral taper,[14,16,19] whereas the remaining three studies used a single pulse of intravenous methylprednisolone (30 mg/kg per day).[15,17,18] Five studies excluded patients with coronary artery abnormalities at baseline,[14–16,18,19] and two studies used Japanese scoring systems to select patients likely to be

	Infliximab	Placebo	p value
Proximal left anterior descending artery *Z* score			
Change at week 2*	−0·61 (−0·81 to 0·40)	−0·31 (−0·51 to 0·11)	0·045
Change at week 5*	−0·8 (−1·03 to −0·57)	−0·51 (−0·73 to −0·28)	0·074
Proximal right coronary artery *Z* score			
Change at week 2*	−0·29 (−0·49 to 0·09)	−0·22 (−0·41 to 0·02)	0·59
Change at week 5*	−0·53 (−0·77 to −0·30)	−0·29 (−0·52 to −0·05)	0·14
Z_{max}†	1·8 (1·5 to 2·0)	1·8 (1·5 to 2·1)	0·87

*Values are reported as mean change (95% CI) from baseline to week 2 and week 5, estimated from the mixed-model repeated measures model. †Z_{max}=largest of the masked, single-observer, echocardiographic measurements of the internal diameter normalised for body surface area of the proximal right coronary artery and left anterior descending artery at weeks 2 and 5 after treatment; values are reported as mean (95% CI) from the multiple linear regression model.

Table 4: **Change from baseline in coronary artery outcomes at weeks 2 and 5 and Z_{max} for the study population by treatment group**

	Infliximab	Placebo	p value
White blood cell count (×10⁹/L)			
24 h	−4·63 (−5·40 to −3·86)	−4·57 (−5·34 to −3·80)	0·91
Week 2	−6·10 (−6·64 to −5·56)	−6·72 (−7·25 to −6·19)	0·11
Absolute neutrophil count (×10⁹/L)			
24 h	−6·18 (−6·89 to −5·47)	−5·02 (−5·74 to −4·30)	0·024
Week 2	−6·52 (−6·91 to −6·14)	−7·05 (−7·44 to −6·66)	0·06
zHgb (SD units)			
24 h	−0·88 (−1·13 to −0·63)	−1·13 (−1·38 to −0·88)	0·17
Week 2	0·39 (0·08–0·71)	0·14 (−0·17 to 0·45)	0·27
Platelet count (×10⁹/L)			
24 h	54·31 (37·95–70·68)	44·27 (27·74–60·81)	0·40
Week 2	79·44 (44·47–114·41)	106·45 (72·41–140·50)	0·28
C-reactive protein (nmol/L)			
24 h	−628·58 (−733·35 to −514·30)	−342·86 (−457·15 to −238·10)	0·0003
Week 2	−1012·21 (−104·76 to −971·45)	−988·59 (−1019·07 to −961·92)	0·37
Erythrocyte sedimentation rate (mm/h)			
Week 2	−23 (−27 to −18)	−14 (−18 to −9)	0·009
Alanine aminotransferase (µkat/L)			
Week 5	−1·22 (−1·27 to −1·17)	−1·24 (−1·27 to −1·19)	0·77
γ-glutamyl transferase (µkat/L)			
Week 5	−1·42 (−1·44 to −1·40)	−1·44 (−1·45 to −1·42)	0·06
Albumin (g/L)			
Week 5	8 (7–9)	8 (7–9)	0·76

zHgb=SD units from the mean for age-adjusted haemoglobin values.[11] *Values are reported as mean change (95% CI) from baseline at 24 h (±4 h), week 2 (study day 14±2 days), and week 5 (study day 35±2 days), estimated from the mixed-model repeated measures model.

Table 5: **Change in laboratory data from baseline at 24 h after completion of intravenous immunoglobulin and at week 2 and week 5 after randomisation by study group**

	Infliximab (n=98)	Placebo (n=98)
Total adverse events	108	128
Probably related to study drug	1	0
Possibly related to study drug	3	5
Participants with ≥1 adverse event	56 (57·1%)	66 (67·4%)
Participants with ≥2 adverse events	32 (32·7%)	32 (32·7%)
Serious adverse events	23	22
Fever*	11	11
Coronary artery abnormality†	6	2
Headache following IVIG infusion	2	1
Haemolytic anaemia following IVIG infusion	2	1
Abdominal pain	0	1
Upper respiratory tract infection	1	0
Desquamating rash	1	0
Burn from hot object	0	1
Seizure*	0	1
Electrolyte abnormality*	0	1
Hepatitis*	0	1
Hypertension*	0	1
Coagulopathy*	0	1
Serious adverse events in infants		
Coronary artery abnormalities	3	2
Fever	2	0
Upper respiratory tract infection	1	0
Participants with ≥1 serious adverse event	22 (22·5%)	17 (17·4%)

Data are n or n (%). IVIG=intravenous immunoglobulin. There were no statistically significant differences in any category of adverse events between the two treatment groups.*One child in the placebo group developed macrophage activation syndrome and had five serious adverse events recorded, including recurrence of fever, hepatitis, hypertension, seizures, and coagulopathy. †Of the ten patients who developed aneurysms, eight had prolonged hospital stays as a result of their aneurysms, which led them to be reported as a serious adverse event.

Table 6: **Adverse events**

Panel: **Research in context**

Systematic review

We searched PubMed for articles in English with a combination of the search terms "Kawasaki disease" and "infliximab". We excluded review articles and evaluated case reports, retrospective comparisons, and clinical trials. We identified several reports worldwide about the use of infliximab for treatment-resistant Kawasaki disease.[7,28–33] A phase 1 trial of second intravenous immunoglobulin versus infliximab for intravenous immunoglobulin-resistant Kawasaki disease showed that infliximab was safe and well tolerated.[8] Subsequently, a retrospective review of intravenous immunoglobulin-resistant patients treated with either a second intravenous immunoglobulin or infliximab showed that patients treated with infliximab had fewer days of fever (median 8 *vs* 10 days, p=0·028) and shorter lengths of hospitalisation (median 5·5 *vs* 6 days, p=0·04) than those treated with a second intravenous immunoglobulin.[9]

Interpretation

Although the addition of infliximab to primary treatment in acute Kawasaki disease did not reduce treatment resistance in this randomised clinical trial, infliximab was shown to be safe and well tolerated, achieved a greater reduction in the left anterior descending coronary artery *Z* score, and reduced the number of days of fever, laboratory markers of inflammation, and intravenous immunoglobulin reaction rates.

intravenous immunoglobulin-resistant.[18,19] Unfortunately, these scoring systems have not successfully identified US children at higher risk of treatment resistance, and clinicians are reluctant to adopt non-selective steroid therapy for all Kawasaki disease patients since most patients are not at risk for sequelae.[2,21]

A North American trial assessed the effect of addition of a single dose of intravenous methylprednisolone (30 mg per kg) to standard intravenous immunoglobulin and aspirin therapy but, because of the overall low rate of coronary artery abnormalities, was unable to show a significant difference in the primary endpoint of the mean Z_{max} score for the right coronary artery and left anterior descending coronary artery combined between groups.[17] In our trial, patients in the infliximab group had a significantly greater mean reduction from baseline in the *Z* score of the left anterior descending coronary artery at week 2 compared with the placebo group (SD −0·6 *vs* −0·3). The small sample size might have precluded detection of other improvements between baseline and subsequent *Z* scores in the infliximab group. Although a *Z* score of 2·5 SD units above the mean normalised for body surface area has been defined as the cutpoint between normal and dilated, use of the patient as his or her own control has been proposed.[22] In a retrospective study of 197 patients with serial echocardiograms up to 12 months after diagnosis, the authors defined a group of 63 patients (32·0%) with occult coronary artery dilation (all *Z* scores <2·5 but acute minus convalescent *Z* score >2 SD units). These patients had higher levels of markers of inflammation at baseline than those without occult dilation, which suggests that patients with a greater change in *Z* score might be at greater risk for more severe arterial damage from Kawasaki disease.[22]

Serum concentrations of the pro-inflammatory cytokine TNFα are raised in patients with acute Kawasaki disease and are higher in patients who develop coronary artery abnormalities.[3,4] Regulatory T cells and tolerogenic myeloid dendritic cells secreting IL-10 are present in acute Kawasaki disease and are more abundant during the sub-acute phase, which suggests that this population might contribute to the self-limited nature of the disease.[23] In a study of a subset of patients enrolled in this trial, we showed that infliximab treatment does not adversely affect generation of tolerogenic myeloid dendritic cells or the development of T cell regulation and memory.[24] In a cohort of 27 patients with active inflammatory bowel disease,

treatment with infliximab enhanced the number and suppressive function of CD4+/CD25+/Foxp3+ regulatory T cells.[25] In patients with rheumatoid arthritis, treatment with infliximab has been shown to increase survival of CD4+/CD25+ regulatory T cells, expand peripherally induced regulatory T cells, and reduce the severity of illness in patients resistant to disease-modifying anti-rheumatic drugs.[26] Thus, infliximab treatment in acute Kawasaki disease could be beneficial by lowering concentrations of this pro-inflammatory cytokine and stimulating the expansion of regulatory T cells.

Complications associated with single-dose infliximab use have not been clearly documented because TNFα blockade is only licensed at present for disorders that need chronic therapy. Prolonged blockade of TNFα over months to years is associated with an increased risk of infection (mycobacteria and fungi), heart failure, and death in people with ischaemic heart disease, lymphoma, and the development of antibodies to infliximab that lead to subsequent allergic reactions.[27] However, single infusions of infliximab were well tolerated by infants and children in our patient population with no severe adverse events attributable to its administration. This was also true in the 11 infants aged 2–11 months who were treated with infliximab in this trial.

The first case report of a child treated with infliximab for Kawasaki disease resistant to several doses of intravenous immunoglobulin and methylprednisolone was published in 2004.[28] Since then, infliximab has been used worldwide for treatment-resistant Kawasaki disease.[7,29–32] These anecdotal reports of one to 20 patients all indicated a benefit with a decrease in clinical signs including fever and markers of inflammation. An analysis of the Paediatric Health Information System database from 2001 to 2006 showed that 14 of the 27 participating hospitals had administered infliximab to 48 patients for treatment-resistant Kawasaki disease.[33] 12 of these 48 patients had received infliximab as part of a phase 1 multicentre, randomised, prospective trial of second intravenous immunoglobulin versus infliximab for intravenous immunoglobulin-resistant Kawasaki disease.[8] This study showed that infliximab was safe and well tolerated. Subsequently, a two-centre retrospective review of intravenous immunoglobulin-resistant patients treated with either a second intravenous immunoglobulin (n=86) or infliximab (n=20) indicated that patients treated with infliximab had fewer days of fever (median 8 *vs* 10 days, p=0·028) and shorter lengths of hospital syay (median 5·5 *vs* 6 days, p=0·04) than those given a second intravenous immunoglobulin.[9] Taken together, these studies suggest that a single infusion of 5 mg per kg of infliximab is safe and well tolerated.

A phase 1 study of 15 children with acute Kawasaki disease showed that addition of etanercept, a TNFα receptor blocker, as a weekly subcutaneous injection for three doses was safe and well tolerated.[6] A multicentre, placebo-controlled, randomised trial to assess etanercept as adjunctive therapy for acute Kawasaki disease is ongoing (ClinicalTrials.gov NCT00841789).

We recognise several strengths and weaknesses of our study. This randomised, double-blind, placebo-controlled trial with central interpretation of echocardiograms and modified intent-to-treat analysis met the gold standard for clinical trial study design and showed more rapid improvement of markers of inflammation and left anterior descending coronary artery *Z* score in patients given infliximab. Our trial is the largest study to assess the safety of one 5 mg per kg dose of infliximab in infants and young children, irrespective of the disorder being treated. The major limitation of our study was the low rate of treatment resistance in the placebo group (11%, compared with historical intravenous immunoglobulin resistance rates of 20%), which decreased our power to detect a difference in the primary outcome measure.

Although the addition of infliximab to primary treatment in acute Kawasaki disease did not reduce treatment resistance, it was safe and well tolerated, achieved a greater reduction in the left anterior descending coronary artery *Z* score, and reduced the number of days of fever, laboratory markers of inflammation, and intravenous immunoglobulin reaction rates.

Contributors

AHT designed the study, collected the data, interpreted the data, and wrote the report. SJ designed the study, did the statistical analysis, and revised the report. PJ designed the study, collected the data, interpreted the data, and revised the report. SJ-F, JMP, JTK, and JPK collected the data and revised the report. XS did the statistical analysis and revised the report. BFP served as the Director of the Echo Core Laboratory, developed the data acquisition protocols for echocardiography, standardised the performance of echocardiograms between the two sites, read all the echocardiograms, and revised the report. OR designed the study, collected the data, interpreted the data, and revised the report. JCB designed the study, collected the data, interpreted the data, and wrote the report.

Declaration of interests

We declare that we have no competing interests.

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