Infliximab is the new kid on the block in Kawasaki disease: a single-centre study over 8 years from North India

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ABSTRACT

This was a single-centre study to evaluate the usefulness of tumour necrosis factor-α (TNF-α) blocker, infliximab (IFX), for treatment of Kawasaki disease (KD) in children in Northern Indian. The study was carried out in the Paediatric Allergy-Immunology Unit, Advanced Paediatrics Centre, Post Graduate Institute of Medical Education and Research, Chandigarh. The study period was January 2007 to March 2015. Review of records of 23 children with KD who had received IFX was carried out. Median age at presentation was 2 years (range 2 months to 12 years). Indications for using IFX were intravenous immunoglobulin (IVIg) resistance (12/23 patients); severe KD especially when coronary artery abnormalities (CAAs) had developed in spite of IVIg (9/23 patients); retinal vasculitis in association with KD (1 patient) and economic reasons (1 patient). Twenty one (21/23) patients had received IVIg (2 g/kg) as first line therapy. A dose of IFX was 5–7 mg/kg given intravenously. Screening tests for tuberculosis (chest x-ray, Tuberculin test, QuantiFERON-TB Gold test) were not carried out prior to IFX infusion in any patient. Duration of follow-up was 0–20 months in 13 patients; 21–40 months in 5 patients and >40 months in 6 patients. Mean follow-up was 28.78±25.49 months, range 1–84 months. Eleven of 12 patients (11/12) who had IVIg resistance showed prompt resolution with IFX. Nineteen patients (19/23) in the cohort had CAAs. Of these, 12 showed improvement over mean follow-up of 28.78±25.49 months (range 1–84 months) and 4 showed normalisation. No adverse reactions were noted during infusion of IFX. On follow-up, none of these patients has developed tuberculosis or any other significant infection over a cummulative follow-up of 662 months. IFX can be considered as a useful adjunct in treatment of children with KD.

Competing interests: none declared.

Introduction

Coronary artery abnormalities (CAAs) occur in 15–25% children with Kawasaki disease (KD). After treatment with intravenous immunoglobulin (IVIg) this figure can be brought down to 3–5% (1-3). However, around 10–20% of patients with KD develop persistent or recrudescent fever after standard therapy with a single infusion of IVIg and aspirin (2, 4). This subset of KD patients is at highest risk for developing CAAs and often warrants additional therapy. It has also been suggested that children with severe forms of KD may benefit from additional immunosuppression with steroids or IFX (5, 6).

IFX reduces fever and coronary artery diameters and is safe and well tolerated (6, 7). However, flare-up of tuberculosis and fungal infections are important concerns in patients treated with IFX (8). There is no information on long-term effects of IFX in children with KD, especially from areas where tuberculosis is endemic.

Patients and methods

The study was carried out in the Paediatric Allergy-Immunology Unit, Advanced Paediatrics Centre, Post Graduate Institute of Medical Education and Research, Chandigarh, North India. Our institute is a teaching hospital funded by the Federal Government and serves as a tertiary care referral centre for North-West India. The work has been approved by the Departmental Publication Review Board.

We have been using IFX in KD since 2007. Review of records of 23 children with KD who had received IFX during the period January 2007 to March 2015 was undertaken for analysis. A total of 331 patients with KD were registered in our clinic during this period. The diagnosis of KD was based on American Heart Association Criteria 2004 (2). Median

age at presentation of our patients was 2 years (range 2 months to 12 years).

At our centre, children with KD receive IVIg (2 g/kg) as single dose along with aspirin (30–50 mg/kg/day) till the child is febrile. Thereafter, aspirin dose is decreased to an anti-platelet dose (3-5 mg/kg/day). Patients with giant aneurysms were given anticoagulation (low molecular weight heparin/ warfarin) along with aspirin. Twenty-one (21/23) patients had received IVIg 2 g/kg as first line therapy. A dose of IFX was 5–7 mg/kg given intravenously. Screening tests for tuberculosis (chest x-ray, Tuberculin test, QuantiFERON-TB Gold test) were not carried out prior to IFX use in any of the patients.

Demographic characteristics such as age and sex, indications of IFX treatment, response and coronary artery outcomes were recorded for all patients. Echocardiography was carried out on Siemens Acuson Sequoia C512 Echocardiography Machine in the Department of Cardiology, Advanced Cardiac Centre.

Thirteen patients had follow-up of up to 20 months, 5 patients had follow-up of 21–40 months and 6 patients had follow-up of more than 40 months. Mean follow-up period was 28.78±25.49 months (range 1–84 months). Total follow-up period was 662 patient months.

Indications for use of IFX in our cohort were as follows:

a) IVIg resistant KD - 12/23 patients.
b) Severe forms of KD especially when CAA have developed in spite of IVIg – 9/23 patients.
c) Retinal vasculitis in association with KD – 1/23 patients (9).
d) Economic reasons – 1/23 patients.

For the latter patient IFX was chosen as first line treatment because the cost of therapy at that body weight was much lower than that of IVIg and the parents were in no position to afford treatment.

Results

Mean age of patients who received IFX was 2.69 years (0.16–12 years, S.D.±2.66). Seven (7/23) patients were infants and the earliest age at presentation was 2 months. There were 16 boys and 7 girls. Mean duration of illness at presentation to our institute was 15.2 ± 9.85 days; mean duration of illness before receiving IVIg was 11.33±7.57 days. Five amongst the 21 patients had received IVIg elsewhere before coming to our institute. Mean duration of illness before administering IFX was 24.04±12.98 days (Table I).

Nineteen patients had CAAs. Of these 2 had ectasia, one had 'bright coronaries' on initial examination and 16 had aneurysms, of which 2 were giant aneurysms.

Outcome

• *IVIg resistant KD*

Eleven of 12 IVIg resistant patients [with (7/9) or without (5/9) CAAs, Table I] responded promptly with resolution of fever and other acute symptoms. In one patient who did not respond to IFX (No. 9, Table I), we had to use pulse intravenous methylprednisolone.

Table I. Showing patient characteristics, indications for IFX and follow-up period in months.

S. no.	Age in years / Sex	Duration of illness (days)	Day of fever on which IVIg was administered	Day of illness on which IFX was administered	Indications for IFX	Months of follow-up	Any significant infections/events on follow-up
1. Am	0.16 /M	12	12	14	IVIg resistant, CAAs	14	None
2. Ad	0.32/M	8	9	14	IVIg resistant, CAAs	25	None
3. Sw	0.32/F	30	22*	31	Severe KD with CAAs (GA)	21	None
4. Ra	0.58/M	10	12	15	IVIg resistant, CAAs	39	None
5. Ja	0.58/M	15	16	22	Severe KD with CAAs	54	None
6. Na	0.66/M	15	16	19	Severe KD with CAAs	16	None
7. Su	0.91/M	60	-	62	Economic reason	72	None
8. Shr	1 /F	32	8*	49	IVIg resistant	28	None
9. Sh	1.5 /F	15	16	22	IVIg resistant**	66	None
10. Ak	2 /M	30	9*	30	IVIg resistant, CAAs	17	None
11. Di	2.5 /M	15	11	45	Severe KD with CAAs (GA)	84	None
12. De	3.5 /F	12	12	15	IVIg resistant	65	None
13. Tu	4 /M	15	19	21	IVIg resistant	63	None
14. Sum	4 /M	8	10	15	IVIg resistant	23	None
15. Vi	4 /M	15	-	20	Retinal vasculitis#	15	None
16. Va	5 /M	20	21	23	Severe KD with CAAs	20	None
17. Ka	6 /F	5	6	10	IVIg resistant	15	None
18. Jas	2 /F	20	8*	23	Severe KD with CAAs	10	None
19. Ri	3 /M	12	12	15	Severe KD with CAAs	5	None
20. Pa	2 /M	30	8*	35	Severe KD with CAAs	3	None
21. Fat	12 /M##	6	6	10	IVIg resistant, CAAs	3	None
22. Van	1 /F	8	8	20	IVIg resistant	3	None
23. Ch	5 /M	20	20	23	Severe KD with CAAs	1	Fever, responded to antimicro-bials

*Had received IVIg outside

**Had received 3 pulses of intravenous methylprednisolone post IFX

#Had received 3 pulses of intravenous methylprednisolone before coming to our institute ##Developed haemorrhagic pericardial effusion with cardiac tamponade during acute phase GA- giant aneurysm.

Table II. Serial coronary artery diameters (in mms.) on echocardiography.

S. no.	1st Echocardiography			2nd Echocardiography			3rd Echocardiography			4th Echocardiography		
	Day	LMCA	LAD	Day	LMCA	LAD	Day	LMCA	LAD	Day	LMCA	LAD
1	14	4.6	3.8	17	4.8	-	8 months	1.5 mm, 3 mm aneurysm at mid LAD		-	-	-
2	11	4.4	4.8	56	4.8	2.2	270	-	1.2	-	-	-
3	30	2.7	8.8	120	2.3	5.2	420	2.4	4.1	-	-	-
4	11	3.5	2.5	14	3.5	1.7	70	1.7	1.2	-	-	-
5	19	4.8	2.2	49	4	2.2	110	3	1.8	-	-	-
6	16	ectatic	-	19	5.8	5.2	45	3.5	1.6	-	-	-
7	60	2.5	1.9	75	2.5	2.3	180	1.7	1.7	-	-	-
8	7	2.7	2	20	Bright CAs		34		1.6	-	-	-
9	19	1.6	1.5	29	1.5	1.6	60	1.5	1.6	-	-	-
10	7	2.1	1.8	12	2.1	1.8	30	4.6	4.8	60	2.1	1.8
11	9	2.7	2.3	17	4.5	4	22	3.3	10	67	2.2	7.7
12	15	-	3	21	6.2	4.1	56	4.5	4.4	150	4.1	1.9
13	19	3.6	2.4	22	4.2	2.4	51	4.1	4.4	210	-	3.5
14	5	-	1.4	47	2.4	2.2	-	-	-	-	-	-
15	19	3.3	1.2	-	-	-	-	-	-	-	-	-
16	18	3.2	7.5	66	3	3.5	-	-	-	-	-	-
17$	7	2.2	-	12	2.4	1.9	13	6	-	150	4.9	3.6
18	8	Normal		22	6	3.8	78	2.3	3.1	-		-
19	13	2.6	3.6 ectasia	60	Normal		-	-	-	-	-	-
20	8	Mild dilatation of LAD and RCA		15	6	6	35	6	6	60	6	5.1
21$$	8	6 diffuse ectasia	3.6	10	3.4	6	50	3.4	6	-	-	-
22	8	3.5, ectasia	2.5	20	2	2.6	40	2	2.4	-	-	-
23$$$	20	3.5	6.8	23	3.7	6.8	30	3.6	6.5	-	-	-

A: Aneurysmal dilatation; G: Giant aneurysm; LMCA: Left main coronary artery; LAD: Left anterior descending artery; RCA: Right coronary artery.
$No CAA on 5th echocardiography after 8 months. $$Had aneurysm in RCA (5 mm) detected on second echocardiography examination.
$$$Had aneurysm in RCA (4.5 mm) and ectatic left circumflex artery on both 1st and 2nd echocardiography examination.

Another patient with giant aneurysms (No. 21, Table I) was started on low molecular weight heparin along with low dose aspirin. He developed haemorrhagic pericardial effusion and cardiac tamponade during the acute phase of illness and required surgical drainage. He showed persistence of coronary artery aneurysms on follow-up (Table II).

• *Severe KD with CAAs*

All 9 patients in this category had received IFX as a second line agent. One patient (No. 19, Table I) had associated thrombocytopenia and hydrops of gall bladder. All patients showed prompt resolution of fever after administration of IFX. No further progression of CAAs was observed among the 2 patients with coronary artery ectasia and in the patient with 'bright coronary arteries' (Table II).

Twelve of 16 patients with coronary artery aneurysms in this cohort had showed reduction in coronary artery diameters on echocardiography done after a mean of 119±112.07 days (range 22–389 days) post-IFX. Four of these patients had subsequent normalisation of coronary artery diameters as assessed on echocardiography. Among the 6 infants with coronary artery aneurysms, 5 showed significant reduction in coronary artery diameter on follow-up (Table II).

• *Retinal vasculitis in association with KD*

This patient (No. 15, Table I) had already received pulse methylprednisolone injections as first line treatment before coming to our institute. He was subsequently given IFX as the retinal vasculitis was still active (9).

• *Economic reasons*

We used IFX as first line treatment in one patient who presented late and IFX was a cheaper alternative to IVIg at that time (No. 7, Table I). The parents were unable to afford therapy. This child too responded well to IFX with prompt subsidence of symptoms and no CAA detected on follow-up.

None of the patients had an infusion related reaction during IFX administration. After a mean follow-up of 28.78±25.49 months (range 1–84 months), none of the patients have developed tuberculosis or any other significant infection. One patient (No. 23, Table I), however, had developed an acute febrile illness 2 weeks after use of IFX which responded well to antimicrobials.

Discussion

It is well known that serum TNF-α plays a significant role in the inflammatory process seen in KD. Concentrations of TNF-α are elevated in the acute phase of KD, and are especially raised in children with severe forms of KD and in those who go on to develop develop CAAs (6, 7, 10). There is, therefore, a sound theoretical basis for using TNF-α antagonists in management of KD. IFX is a chimeric monoclonal antibody that binds specifically to human TNF-α and has been used in patients with KD who have IVIg resist-

Table III. Comparison of present study with other studies on use of IFX in KD.

Author	Number of cases	Median age in years / Sex	CAA	Treatment pre-IFX	IFX dose	Outcome and comments
Burns *et al*., 2005	17	2.6 (0.12-13) (11M/6F)	12/17	All received 2 doses of IVIg; 8/17 MP (1-3 doses)	5 mg/kgx1 (15/17 patients); 10 mg/kg x 1 (2/17 patients)	13/16 defervesced post IFX; 1 patient died of cardiac arrest related to CAA 53 days after IFX
Burns *et al*., 2008	12	-	5/12	Single dose of IVIg (n = 12);	5 mg/kg × 1	11/12 patients receiving IFX after a single IVIG dose defervesced within 24 hours; no serious adverse events
Song *et al*., 2010	16	2.8 (0.2-5.8) (13 M/3F)	9/16	IVIg x2(n=16)	5-6.6 mg/kgX1	Complete response in 13/16 patients; 4/9 had normalisation of CAAs; persistent mild dilatation in 3 and persistent aneurysm in 2; 1 patient developed acute hepatitis during IFX treatment followed by calculous cholecystitis 4 months later.
Mori *et al*., 2012	20	4.6 (1.9-10.5 (10M/10F)	20/20 (mild dilatation of CA)	IVIg 2-4g/kg, PE (n=2). No adverse effects.	5 mg/kgx1	18/20 patients showed defervescence within 24 hours; 2 patients (IFX refractory) underwent PE; only 1 patient had CAL at 30 days post IFX; no severe infections or tuberculosis was observed.
Tremoulet *et al*., 2014	98	3 (1·9–4·8) (60M/38F)	22 had dilatation, 4 had aneurysm	IVIg x1-2 doses	5 mg/kgx1	11/98 had treatment resistance; greater reduction of LAD z score; compared to placebo duration of fever was less. no adverse effects.
Present study	23	2 (0.16-12) (16M/7F)	16/23 had aneurysm, 2 had GA	IVIg x1 in 21/23 and MPx3 in 1	5-7 mg/kg	8/9 IVIg resistant cases had prompt response; 12/16 with CAA had reduction of coronary artery diameters on 119 ± 112.07 days post-IFX; 4/16 had normalisation of coronaries; no patients developed tuberculosis on follow-up; no adverse effects.

M: Male; F: Female; CAA - coronary artery abnormalities; IVIg: intravenous immunoglobulin (2 g/kg unless otherwise stated); MP: methylprednisolone (intravenous pulsed therapy); PE: plasma exchange; CAL: Coronary artery lesion; LAD: Left anterior descending coronary artery.

ant disease. It has also been shown to be of benefit in patients with severe KD when used as an adjunct to IVIg (6, 7, 10, 11). To the best of our knowledge, there is no information on long-term follow-up of IFX in KD, especially in an environment where tuberculosis is endemic. Our study has served to fill up this lacuna in the literature.

We, and others, have previously reported that the phenotype of KD in India is different from that in Japan and western countries (12-14). Mean age of children with KD in India is higher, male predominance is more marked and periungual desquamation appears earlier. It is possible that these phenotypic differences could be due to a different genetic make-up of the Indian population. It is also entirely plausible that this genetic make-up may influence the response to IFX in a given population. On administration of IFX, we noted prompt resolution of fever in 11/12 (91.67%) patients with IVIg resistant KD (Table III). Only one patient in our series required additional therapy with pulse methylprednisolone injections (No. 9, Table I). In 2005, Burns *et al*. were the first to study use of IFX in KD in a systematic manner (15). They noted prompt defervescence of fever in 13/16 patients with KD after IFX (14). Hirono *et al*. (16) and Song *et al*. (17) have subsequently published their experience with IFX and found equally efficacious results (Table III).

Son *et al*. (18) found that although administration of IFX resulted in fewer febrile days as well as fewer days in hospital, it did not result in improved coronary artery outcomes. Twelve of the 16 (75%) patients with CAAs in our study showed no further progression. In addition we documented reduction in coronary diameters after a mean follow-up of 119±112.07 days (Table II). The 2 children with giant aneurysms (No. 3 and 11, Table II) showed reduction in the size of aneurysms after 3 and 1 months of follow-up respectively. Four out of 16 (25%) patients showed normalisation of coronary diameters on follow-up. The 2 patients with coronary ectasia in our cohort showed no further progression after IFX. Tremoulet *et al*. (5) reported a greater reduction in the left anterior descending coronary artery Z score post IFX. Song *et al*. (17) reported that, out of 13 patients on follow-up (median follow-up 5 months), 9 had CAAs and 4 (44%) had subsequent normalisation post IFX. Stenbog *et al*. (19) also observed regression of coronary artery lesions post IFX. Similarly, Brogan *et al*. (20), reported partial resolution of CAAs on echocardiography done 5 months post IFX. Mori *et al*. (21) also reported similar findings (Table III).

We have used IFX as pre-emptive therapy in 2 patients. One of these had presented late in the course of the disease but had continuing fever and raised acute phase parameters (No. 7, Table I). At his weight, the cost of IVIg was

much more than that of IFX. As the parents could not afford IVIg, he was given IFX as pre-emptive therapy after counselling. The other patient had developed retinal vasculitis (No. 15, Table I) during the acute phase of KD and had not shown improvement with methylprednisolone that had been administered elsewhere prior to his admission in our unit (9). Both patients responded to IFX.

It is noteworthy that none of our patients have developed any significant adverse reactions following IFX. This has also been the experience of several other workers (6, 11, 15, 21). Tremoulet *et al*. have reported that, if IFX is administered prior to IVIg, the risk of infusion reactions related to IVIg can be significantly decreased (6). In the study by Song *et al*. (17), 1 patient had developed acute hepatitis during IFX treatment followed by calculous cholecystitis 4 months later. Oishi *et al*. (22) also reported 1 case that developed transient urticaria post IFX. Based on results of our study as well as reports from other centres, it can be surmised that IFX does not appear to have significant adverse reactions when used in the setting of KD.

Our study reports a total of 662 patient months follow-up on IFX use in children with KD. To the best of our knowledge this is the largest single-centre follow-up experience with IFX in KD reported so far. We did not screen our patients for tuberculosis before administration of IFX as only one dose was envisaged. Moreover, the drug had to be administered on an emergent basis when the children were still febrile and very sick. Under these circumstances it would have been inappropriate to wait for 72 hours to read the tuberculin reaction before giving IFX. The fact that none of these patients developed tuberculosis, or any other significant infection, during follow-up reiterates the fact that single dose IFX appears to be safe even in a clinical setting where tuberculosis is endemic. One of our patients did present with an acute febrile illness 2 weeks post IFX. This responded promptly to antimicrobials and it would be conjectural to relate it to IFX.

Our study shows that IFX is a safe and useful adjunct in the treatment of KD. This is a significant finding as IVIg alone fails to prevent coronary damage in at least 5–10% patients (1-3). There are, however, some limitations to this work and these must be kept in mind before one draws conclusions. Our sample size was small and the study was retrospective in nature. We have not given Z-scores for coronary artery diameters as our work spans over 8 years and we were not recording these scores during the early part of the study. In addition, we did not assay the pro-inflammatory cytokines in any of our patients and we have not addressed some of the other issues linked to long-term follow-up of children with KD (23).

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