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Infliximab Treatment for Refractory Kawasaki Disease in Korean Children

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ABSTRACT

Background and Objectives: This was a multicenter study to evaluate the usefulness of the tumor necrosis factor-alpha (TNF- α) blocker infliximab for treatment of Korean pediatric patients with refractory Kawasaki disease (KD). **Subjects and Methods:** Data from 16 patients throughout Korea who were diagnosed with refractory KD and received infliximab were collected retrospectively. **Results:** Complete response to therapy with cessation of fever occurred in 13 of 16 patients. C-reactive protein (CRP) concentrations decreased following infliximab infusion in all 14 patients in whom it was measured before and after treatment. There were no infusion reactions or complications associated with infliximab except in 1 case with acute hepatitis occurring during treatment followed by calculous cholecystitis 4 months later. Fifteen patients had coronary artery (CA) abnormalities before infliximab therapy. Three had transient mild dilatation and 9 had CA aneurysms, with subsequent normalization in 4 patients, persistent mild dilatation in 3, persistent aneurysm in 2, and there were 3 cases (2 with CA aneurysm, 1 with mild CA dilatation) without follow-up echocardiography. **Conclusion:** The results of this study suggest that infliximab may be useful in the treatment of refractory KD, and it appears that there is no significant further progression of CA lesions developing after infliximab treatment. Multicenter trials with larger numbers of patients and long-term follow-up are necessary to assess the clinical efficacy and safety of infliximab in refractory KD. (**Korean Circ J 2010;40:334-338**)

KEY WORDS: Infliximab; Kawasaki disease.

Introduction

Coronary artery (CA) lesions, including dilatation and aneurysms, develop in 15% to 25% of children with untreated

Kawasaki disease (KD).^{1,2)} Administration of intravenous immunoglobulin (IVIG) is now well accepted as the standard treatment for KD, and reduces the risk of coronary artery aneurysm (CAA) to 3% to 5%.^{3,4)} Approximately 10% to 20% of patients with KD fail to become afebrile after the first dose of IVIG,^{5,6)} and the current practice for these patients is to administer repeated doses of IVIG. However, of the patients who still remain febrile after repeated doses of IVIG, no large randomized controlled clinical trial has established their optimal management.⁵⁾ These refractory KD patients are at a much higher risk for developing CAA. The KD patients refractory to IVIG were reported to improve and defervesce after steroid therapy in several series,⁷⁾ but there are several reports concerning the adverse effects of steroid treatment. No controlled clinical trials have estab-

Received: December 28, 2009

Revision Received: January 19, 2010

Accepted: February 9, 2010

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lished their optimal use in managing refractory patients.

Even less data is published on the use of other therapies, which may include 1 or more repeat doses of IVIG, high-dose pulse methylprednisolone (MP), cyclophosphamide, methotrexate, or plasmapheresis in IVIG-refractory KD.⁸⁾⁹⁾ Recently, infliximab (Remicade), a monoclonal antibody that blocks the biological activity of tumor necrosis factor-alpha (TNF- α), was used in a few refractory KD patients and reported to be effective and safe.⁸⁾¹⁰⁾

Subjects and Methods

Refractory KD was defined as the persistence or reappearance of fever ($\geq 38.0^{\circ}\text{C}$ or 100.4°F) at least 36 hours after the last of more than 2 doses of IVIG therapy and high-dose aspirin with or without intravenous MP pulse therapy (30 mg/kg/dose/day). Complete response was defined as the cessation of fever within 12 hours of infliximab infusion therapy.

Sixteen cases were retrospectively collected from clinicians throughout Korea who had used infliximab, a monoclonal antibody against TNF- α , for patients with refractory KD between July 2004 and November 2008.

Sixteen patients with acute KD (13 males, 3 females, median age 2.8 years, range 0.2-5.8 years) received infliximab infusion after at least 2 doses of IVIG and daily aspirin (50-100 mg/kg/day) with or without MP pulse therapy for the following indications: 1) persistent or recrudescing fever (14 patients) and 2) fever plus persistent arthritis (2 patients) (Table 1).

All 16 patients were Korean. All patients had prolonged fever and met either 4 of the 5 standard criteria for KD or 3 of the 5 criteria in addition to CAA by echocardiography.⁹⁾

Demographic characteristics, therapies administered, C-reactive protein (CRP) concentrations before and after infliximab treatment, infliximab dose, response, and coronary artery (CA) outcomes were recorded for all patients. Illness day 1 was defined as the first day of fever.

The internal diameter of the CA measured by transthoracic echocardiography was defined as aneurysm with the following parameters: 1) if the internal lumen diameter was >3 mm in children <5 years old or >4 mm in children >5 years old; 2) if the internal diameter of a measured segment was >1.5 times that of an adjacent segment; or 3) if the coronary lumen was clearly irregular by the Japanese Ministry of Health criteria classification.¹⁰⁾¹¹⁾ CA dilatation was defined as CA size larger than normal for age, but no apparent segmental aneurysm. Aneurysms were identified as saccular or fusiform.

Results

Treatment and patient outcomes

All patients received more than 2 doses of IVIG. Three patients received more than 3 doses of IVIG (2 g/kg/dose/day), and 11 patients received more than 2 doses of IVIG and MP pulse therapy (30 mg/kg/dose/day).

All patients failed to become persistently afebrile following these treatments. Before infliximab therapy, the patients

Table 1. Patient characteristics and outcomes

Patient number	Age (year)	Sex	1st IVIG (day)	Illness day at treatment	Response*	Other treatment	Oral steroid (Y/N)	Comment
1	3.5	M	5	11	Complete	IVIG \times 2, MP \times 4	N	
2	1.3	M	5	8	No	IVIG \times 3	N	One more IVIG
3	4.6	F	5	16	Complete	IVIG \times 2, MP \times 2	N	
4	1.1	M	3	10	Complete	IVIG \times 3, MP \times 3	N	
5	5.4	M	5	25	Complete	IVIG \times 4, MP \times 4	N	Arthralgia
6	0.3	M	4	29	Complete	IVIG \times 2, MP \times 3	Y	Hepatitis, Cholecystitis
7	2.4	F	5	16	Complete	IVIG \times 2, MP \times 3	N	
8	2.0	M	5	16	Complete	IVIG \times 2, MP \times 2	Y	
9	0.7	M	4	6	No	IVIG \times 2	Y	
10	4.7	M	5	21	Complete	IVIG \times 2, MP \times 1	N	Arthralgia
11	0.2	M	6	16, 40	No	IVIG \times 2, MP \times 3	Y	One more infliximab
12	3.9	M	4	19	Complete	IVIG \times 2, MP \times 3	Y	
13	15.0	M	3	20	Complete	IVIG \times 2, MP \times 3	N	
14	2.4	F	4	21	Complete	IVIG \times 2	N	
15	5.8	M	5	21	Complete	IVIG \times 2	N	
16	2.8	M	5	10	Complete	IVIG \times 2	N	

*Complete response: afebrile within 12 hours of infliximab infusion with complete resolution of clinical signs and symptoms. IVIG: intravenous immunoglobulin, MP: intravenous methylprednisolone, 30 mg/kg/dose

Table 2. CRP values and echocardiographic findings of coronary artery

Patient number	CRP (before/after) (mg/dL)	Echo on treatment (RCA/LCA) (mm/mm)*	Echo on follow up (RCA/LCA) {mm/mm (month)}
1	20.6/12.7	9.0/5.0	6.0/4.0 (28)
2	5.9/NA	WNL/3.1	WNL/WNL (2)
3	8.5/2.9	WNL/3.3	WNL/WNL (2)
4	4.3/<0.3	4.3/4.6	2.6/2.9 (5)
5	4.7/2.6	3.5/5.0	2.0/2.0 (5)
6	9.1/1.9	3.5/4.5	2.8/2.9 (24)
7	3.9/0.6	3.3/3.6	2.5/2.5 (7)
8	4.4/1.0	7.0/9.0	NA
9	8.6/6.8	4.5/3.5	2.6/2.9 (7)
10	5.1/3.4	5.0/4.8	3.5/3.2 (2)
11	15.9/0.7	5.2/5.5	4.0/4.0 (4)
12	5.6/NA	1.7/3.2	1.7/2.3 (2)
13	12.0/0.5	4.6/3.9	2.7/2.7 (12)
14	21.9/13.7	3.0/2.8	NA
15	12.6/3.8	5.0/4.0	NA
16	13.3/5.7	2.1/2.5	2.0/2.5 (2)

*Month: interval until follow-up echocardiography. CRP: C-reactive protein, LCA: left coronary artery, NA: not available, RCA: right coronary artery

had been either persistently or intermittently febrile for 6 to 40 days. Each of the 16 patients received a single infusion of 5-6.6 mg/kg of infliximab, with tapering of oral prednisolone in 5 patients. Complete response occurred in 13 of the 16 patients, including 2 patients who achieved both resolution of fever and accompanying persistent arthritis. There were 3 patients who did not achieve complete response. In patient no. 2, his fever subsided after infliximab infusion, but he was readmitted to another hospital because of recrudescing fever which responded to a fourth dose of IVIG. In patient no. 9, the frequency and severity of his fever decreased from 3-4 times per day at higher than 38.5°C, to 1 time per day at around 38°C for 3 days after infliximab therapy. His fever subsided after 1 additional dose of intravenous MP pulse therapy, followed by tapering of oral prednisolone. In patient no. 11, his fever subsided after infliximab therapy, but it recurred 24 days later, after the cessation of oral prednisolone therapy.

Two patients (no. 5 and no. 10) with fever and arthritis treated with infliximab, achieved dramatic and permanent resolution of their arthritis within 12 hours of the infusion. In one, infliximab was administered for persistent mild fever and severe arthritis, and his arthritis resolved dramatically. Likewise, in the other, high fever and persistent arthralgia resolved dramatically after infliximab treatment.

There were no infusion reactions to infliximab. However, in patient no. 6, acute hepatitis occurred during infliximab treatment; this was followed by calculous cholecystitis 4 months later, which was managed by supportive care (Table 1).

Changes in C-reactive protein concentrations

Pretreatment levels were determined within 24 hours before infliximab infusion, and posttreatment levels within 72 hours after infusion. All 16 patients had elevated CRP concentrations before infliximab infusion, which decreased following infusion in all 14 patients for whom data was obtainable (Table 2).

Echocardiographic findings of coronary arteries

Echocardiographic determinations of the maximum internal diameters of the right and left CAs performed at any time during the disease course are shown in Table 2.

Fifteen patients had CA abnormalities (from mild CA dilatation to aneurysm) documented by echocardiography before infliximab therapy. Thirteen patients were followed up for 2 to 28 months (median follow-up: 5 months), and 3 cases were without follow-up. Three had transient mild CA dilatation that resolved after infliximab infusion, and 9 had CAA with subsequent normalization in 4 patients, persistent mild dilatation in 3, and persistent aneurysm in 2 on follow-up echocardiography. Of 3 cases without follow-up echocardiography, 2 had CAA and 1 had mild CA dilatation (Table 2).

Discussion

Although IVIG with aspirin therapy is effective for acute KD, numerous series have documented a 10% to 20% failure rate with persistence of fever and clinical and laboratory signs of inflammation.⁵⁾⁽⁸⁾⁽¹²⁾ While a second infusion of IVIG (2 g/

kg) is strongly recommended in all children with persistent or recrudescing fever, proposals are lacking on how to treat the small group of refractory KD (3-4%) still remaining febrile (up to one-third of IVIG-retreated patients).^{12,13} There are different therapeutic approaches, including either a third dose of IVIG (2 g/kg) or pulse MP, although patients failing to respond to a second infusion of IVIG seem to be refractory to a third dose.¹³⁻¹⁵ Some have identified predictors of IVIG nonresponsiveness.¹⁶ But others have found no significant differences in characteristics between responders and non-responders.¹⁷ A study found that very early treatment of KD is likely to result in greater need for additional IVIG compared to conventional treatment.¹⁸

The use of corticosteroids in KD remains controversial. Reluctance to use corticosteroids for KD dates to Kato's study in 1979, in the pre-IVIG era.¹⁹ Others have reported the use of both intravenous MP and oral corticosteroids with good results, predominantly in patients with refractory disease.²⁰ Recent reports on the use of corticosteroids as "rescue therapy" in IVIG-refractory KD have not shown an association between corticosteroids and an increase in CAA.⁷ However, treating refractory KD with corticosteroids should be undertaken with caution. The possible transient adverse effects of corticosteroids include sinus bradycardia, hyperglycaemia, and hypertension.²¹ In addition, even though fever initially resolved faster in patients receiving intravenous MP, there was a tendency for fever to recur later in MP-resistant patients, which delayed therapeutic decision-making, and ultimately the final resolution of fever.²² Steroid treatment has also been reported to be a risk for development of CAA and rupture.⁴

Infliximab is indicated for treating immune-modulated inflammatory disorders, including pediatric Crohn's disease and juvenile idiopathic arthritis.^{23,24} In a recent study of infliximab therapy in patients with KD who failed to respond to repeated IVIG infusions, patients demonstrated dramatic improvement with no adverse events.^{8,10}

It is thought to be beneficial in KD because TNF- α may be involved in the inflammatory process in acute KD. And recently, Hirono et al.²⁵ showed that serum concentrations of interleukin-6 and soluble TNF receptor-1 dramatically decreased after infliximab treatment, and correlated with serum CRP concentrations and fevers. Hui-Yuen et al.²⁶ have shown that TNF- α is necessary for the development of CA lesions in an animal model of KD.

Burns et al.⁸ reported that complete response to infliximab therapy with cessation of fever occurred in 14 of 16 patients. Hirono et al.²⁵ reported that complete response to therapy with cessation of fever occurred in 8 of 11 patients. In our study, 13 of 16 patients (about 80%) had complete response. CRP concentrations were elevated in all patients before infliximab infusion, and following the infusion they were lower in 14 patients in whom the concentrations were again de-

termined within 48 hours of treatment.

In our series, 2 patients with fever and arthritis treated with infliximab achieved dramatic resolution of their arthritis and fever within 12 hours of the infusion. Arthritis or arthralgia can occur in patients in the acute or subacute stage of KD. A minority of patients suffer from severe intractable arthritis or arthralgia. As with our cases, in those patients infliximab may prove useful.

Based on current reports, the risk of development of CAA is highest in the group of patients who do not respond to a single dose of IVIG. We saw rapidly progressive CA dilatation on frequent follow-up echocardiography in 4 refractory KD patients during MP pulse therapy. CA dilatation stopped, or the rate of progression at least slowed after infliximab treatment. It may be that there is no significant additional progression of CA lesions after infliximab treatment, and that infliximab treatment for refractory KD may prevent rapidly progressive CA dilatation. Fortunately, we did not have a fatal case. But there have been several fatal cases due to rapidly progressive CA dilatation with subsequent rupture.⁴

We recommend that for a patient with refractory KD, frequent follow-up echocardiography is mandatory, and if a CAA progresses rapidly despite other therapies, including MP, early administration of infliximab should be considered.

Serum concentrations of the proinflammatory cytokine TNF- α are elevated in CA disease and acute KD patients.^{26,27} Therefore, it has been postulated that TNF- α blockade might be effective in the control of inflammation in patients with KD who fail to respond to IVIG. In our study, the cessation of fever and decrease in CRP levels following TNF- α blockade by infliximab treatment suggest that TNF- α is indeed an important mediator of inflammation in this vasculitis. The success of TNF- α blockade in most patients in this study further supports the central role of TNF- α in KD pathogenesis.

The pharmacodynamics, pharmacokinetics, and safety of infliximab in children have not yet been fully established. Similarly, the appropriate dose of infliximab for controlling inflammation in acute KD has not been determined. A dose of 5 mg/kg was used in the majority of patients in this series by extrapolation from data generated in pediatric patients with juvenile idiopathic arthritis and Crohn's disease.^{8,23,24}

Other considerations regarding infliximab therapy for refractory KD include cost and safety. The most common symptoms of immediate infusion reactions have been flushing and shortness of breath.²⁸ No infusion reactions were noted in our series. Complications of infliximab administration include reactivation of latent tuberculosis, histoplasmosis, increased risk of bacterial sepsis and lymphoma, development of antinuclear antibodies, and heart failure.^{8,29,30} There was only one mild complication in our series; acute hepatitis occurred during treatment and calculous cholecystitis occurred 4 months later, which subsided with supportive care.

Concentrations of antibody to infliximab were not measured in our study. Antibody formation should not be a problem in KD, because usually only 1 dose of infliximab is needed. Because infliximab is administered only once for most patients with refractory KD, its administration may cause fewer complications in KD patients than in patients with Crohn's disease or juvenile idiopathic arthritis, where it is administered repeatedly.

Even though infliximab is efficacious but not without possible complications, we recommend it as second-line therapy for KD cases that are refractory to conventional therapy, until the results of long-term studies are available. However, we cautiously propose that early administration of infliximab rather than a second IVIG treatment should be considered for patients with rapidly progressive CA dilatation.

The limitations of this study include its retrospective nature, small number of patients, and the use of multiple different therapies following the first IVIG treatment failure. In addition, we did not determine proinflammatory cytokine concentrations before and after infliximab treatment. Different IVIG preparations were used at each center. Concomitant anti-inflammatory therapies administered to several of these patients made it difficult to assess the effects of infliximab.

In conclusion, our study suggests that infliximab can be useful not only in the treatment of refractory KD but also in the prevention of progression of CA lesions. There were no infusion reactions and complications attributed to infliximab administration in 15 of 16 patients. Multicenter trials with a larger number of patients and long-term follow-up are necessary to assess the clinical efficacy and safety of infliximab for refractory KD.

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