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Antimicrobial therapy using sulfamethoxazole trimethoprim for Kawasaki disease patients unresponsive to intravenous immunoglobulin

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ABSTRACT

Our previous study suggested that the production of superantigens and heat-shock protein 60 by small intestinal bacteria might play a role in Kawasaki disease (KD). We demonstrated that they were all resistant to commonly used antibiotics, except for sulfamethoxazole trimethoprim (SMX-TMP). We used SMX-TMP for 7 cases of KD that were unresponsive to intravenous immunoglobulin (IVIG) and studied the antipyretic potency of this treatment. In 6 out of the 7 cases, we demonstrated that antipyretic potency was observed without side effects within 2 days of the initial administration. Antimicrobial therapy using SMX-TMP might represent a novel strategy for cases of KD that are unresponsive to IVIG.

Keywords: Antimicrobial Therapy; Intravenous Immunoglobulin Resistance; Kawasaki Disease; Sulfamethoxazole Trimethoprim

1. INTRODUCTION

Immunoglobulin is helpful during the acute phase of Kawasaki disease (KD), but there is an approximate 5% failure rate, and close to a 30% adverse effect rate. In addition, immunoglobulin is expensive, at approximately $100 per gram [1]. Antibiotic treatments targeting the causative bacteria may be a more effective and economical treatment for KD if the detailed pathogenic mechanism of the disease can be elucidated. In our previous study, we found some particular Gram-negative microbes producing heat-shock protein 60 and several Gram-positive cocci having superantigenic properties on the surface of the gastrointestinal tract which might play a role in the onset of Kawasaki disease (KD) [2]. We performed antibiotic sensitivity testing on these strains, considering them to be the cause of this disease if they participated in the onset, and found that they were all resistant to all of the commonly used antibiotics except for sulfamethoxazole trimethoprim (SMX-TMP). In this study, we used SMX-TMP for 7 cases of KD that were unresponsive to intravenous immunoglobulin (IVIG) and studied the antipyretic potency of this treatment.

2. CASE SERIES

We identified seven patients with intractable IVIG-refractory KD at Juntendo University and its two branch hospitals between January 2008 and February 2009 who were treated with 2 courses of IVIG at a dose of 2 g/kg given over 24 hours and 1 course of pulsed intravenous methylprednisolone (IVP: methylprednisolone intravenously at a dose of 30 mg/kg/day given up to a maximum 1000 mg/day) therapy. This trial was approved by the Juntendo University Review Board.

The demographic characteristics of the 7 patients described in this report are summarized in **Table 1**. All of the cases had received primary IVIG therapy but experienced no decline of fever within 24 hours from the end of the infusion, and were therefore defined as unresponsive cases. Three of the cases had received additional IVIG therapy, and 4 had received IVP therapy. However, in all of the cases, the patients did not respond to the secondary therapy and did not experience any decrease in their fever within 24 hours after treatment, and therefore, underwent tertiary therapy.

For the tertiary therapy, IVP was selected for the patients who had consecutively received IVIG therapy twice, and IVIG was selected for the patients who had received IVP therapy during the second round of treatment. However, because all 7 cases were resistant to

Table 1. Demographic characteristics of the patients with Kawasaki disease.

Case	Age	Sex	Treatment			Hospital day of the 1st treatment	PSL used concomitantly with SMX-TMP
			1st	2nd	3rd		
1	5 m	M	IVIG	IVP	IVIG	5	2 mg/kg/d
2	10 m	M	IVIG	IVP	IVIG	5	1 mg/kg/d
3	2 y 4 m	M	IVIG	IVP	IVIG	5	2 mg/kg/d
4	4 y 6 m	M	IVIG	IVIG	IVP	4	1 mg/kg/d
5	5 y 3 m	M	IVIG	IVIG	IVP	5	1 mg/kg/d
6	10 m	F	IVIG	IVIG	IVP	7	2 mg/kg/d
7	2 y 3 m	F	IVIG	IVP	IVIG	5	1 mg/kg/d

SMX-TMP: sulfamethoxazole trimethoprim; IVIG; intravenous immunoglobulin; IVP: pulsed intravenous methylprednisolone; PSL: prednisolone.

Table 2. Clinical characteristics of the patients with Kawasaki disease.

Case	Duration of fever (days)		CRP value (mg/dl)		Maximum coronary artery z-scores*	
	Until SMX-TMP use	After SMX-TMP use	Before SMX-TMP use	1 week after SMX-TMP use	Before SMX-TMP use	1month after SMX-TMP use
1	11	1	6.9	4.7	15.7	11.2
2	12	2	12.1	8.2	14.6	6.0
3	11	2	10.6	6.1	12.6	0.8
4	11	1	12.3	6.8	7.0	3.5
5	10	1	13.2	7.3	6.5	3.1
6	19	8	16.4	17.2	21.0	28.0
7	12	2	11.3	7.8	12.7	4.8

SMX-TMP: sulfamethoxazole trimethoprim; CRP: C reactive protein; *: maximum coronary artery z score was defined as the larger of the proximal left anterior descending coronary artery and the proximal right coronary artery z scores adjusted by body surface area [4].

these therapies as well, and no decrease in fever was observed for 24 hours or more, one of the authors (SN) was consulted, and upon receiving authorization from the families of the patients, the use of SMX-TMP was attempted.

At the time of the consult, 5 of the 7 cases already had coronary artery aneurysms, and in 1 case that had been diagnosed and treated late, giant aneurysms had formed. In blood tests of the patients performed immediately before starting SMX-TMP administration, the C reactive protein (CRP) values were 6.9 to 16.4 mg/dl (mean: 11.8). In all cases, SMX-TMP was orally administered 2 times per day at a dose of 0.04 g/kg/time, which is the general dose for infants, for 5 consecutive days. For concomitant treatment, aspirin was administered 3 times per day at 10 mg/kg/time, and prednisolone was administered orally at 1 - 2 mg/kg/day as supportive therapy for IVP.

After SMX-TMP administration, a decline in fever was observed within 2 days (mean: 1.5 days) in 6 out of the 7 cases (**Table 2**). In the case that had formed giant aneurysms, a decrease in the fever was observed after 8 days. In the blood tests of the patients taken 1 week after SMX-TMP administration, the CRP values were 4.7 to 17.2 mg/dL (mean: 8.3). At 2 weeks after SMX-TMP administration, the coronary lesions had undergone either minimal growth or had regressed, with the exception of the 1 case that had formed giant aneurysms. In this case, an enlargement of the aneurysms was observed. In all of the cases, no side effects that were believed to have been caused by SMX-TMP were observed during the course of treatment or follow-up.

3. DISCUSSION

It is often considered common knowledge that antimicrobial agents are ineffective for KD [3]. In 6 of the 7 cases described in this study, the KD was unresponsive to IVIG, but there was a decrease in fever within 2 days of starting SMX-TMP administration. Because concomitant drugs were used only for supportive therapy, these results suggest that the declines in fever were induced by the SMX-TMP. In addition to the decrease in fever, the CRP values also decreased, and the progression of coronary aneurysms also appeared to have been suppressed. The high efficacy of SMX-TMP was probably due to the fact that several types of pathogenic bacteria that were hypothesized to have triggered the onset of KD were sensitive to SMX-TMP. The case that had formed giant aneurysms required 8 days for the fever to subside after initiating SMX-TMP treatment, so it is difficult to conclude whether the SMX-TMP treatment was effective for that patient. In this case, it is possible that the pathogens were not sensitive to SMX-TMP, or that the window for administration had been missed.

SMX-TMP is used throughout the world, particularly for the purpose of preventing infections in hypoimmune infants undergoing chemotherapy [5-6]. In the 7 cases described in this study, no side effects were observed, although adverse effects associated with SMX-TMP on the hematopoietic system, etc. are not rare, and the safety of the agent for young infants has not been established [7]. Therefore, there remain a number of problems to be resolved in terms of safety in order for SMX-TMP to be frequently used for treating KD, which often involves infant patients. Moreover, if SMX-TMP is used frequently, this raises the problem of the development of resistance by the pathogenic bacteria. Therefore, as a method for treating cases that are unresponsive to IVIG, SMX-TMP may only provide a temporary solution. However, it is an undeniable fact that there are cases of KD that are resistant to IVIG and IVP [8-10], and the discovery of an effective antimicrobial therapy is believed to be a significant step toward reducing the number of cases of myocardial infarction caused by KD.

Although our results are promising, this study does not go beyond the realm of case reports, and in order to determine which antimicrobial agents are effective for cases of KD that are unresponsive to IVIG, further evidence from randomized control trials will be needed.

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