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Pentoxifylline and intravenous gamma globulin combination therapy for acute Kawasaki disease

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Abstract We compared the efficacy of oral administration of pentoxifylline (PTX) and intravenous infusions of gamma globulin (IVGG) combination therapy with that of IVGG in reducing the frequency of coronary-artery lesions (CAL) in children with Kawasaki disease (KD), in a randomized trial. All patients with KD received acetylsalicylic acid (30 mg/kg per day), until the 30th day, after the onset of fever, followed by daily acetylsalicylic acid at a dose of 3–5 mg/kg per day thereafter, and intravenous IVGG, 200 mg/kg per day, for 5 consecutive days. In addition, patients randomly assigned to PTX and IVGG combination therapy groups received oral PTX at a dosage of 10 mg/kg per day (low-dose) or 20 mg/kg per day (high-dose), in three divided doses until the 30th day. Patients with KD were all free from CAL prior to treatment. We assessed the presence of CAL by two-dimensional echocardiography which was also done prior to treatment and then twice a week after hospital admission. We detected CAL in 3 of 18 patients (16.7%) in the IVGG therapy group, as compared with 2 of 18 patients (11.1%) in the low-dose PTX and IVGG combination therapy group. There were no significant differences between the two groups. In the next study, we detected CAL in 3 of 21 patients (14.3%) in the IVGG therapy group, as compared with none of 22 patients (0%) in the high-dose PTX and IVGG combination therapy group ($\chi^2 = 6.4$, $P < 0.02$). No adverse side-effects were observed in 79 patients with KD.

Conclusion Despite a small number of patients, we believe that oral administration of high-dose PTX and intravenous infusions of IVGG combination therapy is safe and effective in reducing the incidence of CAL when administered early in the course of KD.

Key words Kawasaki disease
Coronary-artery lesions
Pentoxifylline therapy · Tumour necrosis factor α

Abbreviations *CAL* coronary-artery lesions · *IVGG* intravenous infusions of gamma globulin · *KD* Kawasaki disease · *PTX* pentoxifylline · *TNFα* tumour necrosis factor α · *TNF-R* TNF receptor

Introduction

Kawasaki disease (KD) is an acute illness that occurs predominantly in infancy and early childhood [13]. Coronary-artery aneurysm or ectasia develops in approximately 15%–25% of children with the disease [12, 19]. Conventional therapy for KD includes acetylsalicylic acid as an anti-inflammatory and antithrombotic agent, and high-dose intravenous gamma globulin (IVGG) to prevent

coronary abnormalities [10, 14]. Although the incidence of coronary artery lesions (CAL) in KD has declined since the routine application of IVGG treatment, it still develops in approximately 10% of patients with KD in Japan [16].

Tumour necrosis factor α (TNFα) is an inducible cytokine produced primarily by monocytes/macrophages. Many biological activities of TNFα appear to be involved in the pathogenesis of inflammation and vasculitis. Recently we have reported that patients with KD and high soluble TNF receptor (TNF-R) levels in serum seem to be susceptible to CAL even if they receive IVGG therapy [9]. Soluble TNF-R levels in serum reflect the biological activity of TNFα [2, 17]. Therapeutic modulation of the regulatory system of TNFα, may be effective in acute KD.

Here we report the effect of a randomized trial of pentoxifylline (PTX) and IVGG combination therapy as compared with IVGG therapy on the frequency of CAL and the severity of systemic inflammation in patients with KD. PTX blocks TNFα production in lipopolysaccharide-treated macrophages and in endotoxin-treated human volunteers, and has been used for treating diseases with the increased TNFα production [1, 11, 18, 21].

Patients and methods

Patients

The treatment protocol consists of two parts, study-1 and study-2. We enrolled subjects from March 1991 to January 1992 in study-1, and from February 1992 to June 1993 in study-2. The treatment protocol in study-2 used high-dose of PTX.

Study-1 included 19 boys and 17 girls, aged from 2 months to 7 years 11 months. Study-2 included 24 boys and 19 girls, aged from 2 months to 6 years 5 months. Each child who met the criteria for diagnosis and who came to our hospitals within 10 days of the onset of illness entered the study. The 1st day of fever was taken to be the 1st day of disease. Children were all free from CAL prior to treatment and randomly allocated to therapy groups PTX and IVGG combination (group P_1 in study-1 and group P_2 in study-2) and IVGG only (group G_1 in study-1 and group G_2 in study-2). Their parents gave informed consent before their participation in the study.

Study design

Patients were randomly divided into two therapy groups in study-1 and study-2, respectively. Group G_1 and G_2 received acetylsalicylic acid (30 mg/kg per day) in three divided doses until the 30th day, after the onset of fever, followed by daily acetylsalicylic acid at a dose 3–5 mg/kg per day thereafter, and intravenous infusions of IVGG (Venilon, Teijin Limited, Tokyo) as a 5% solution at a daily dosage of 200 mg/kg for 5 consecutive days. The Research Committee on Kawasaki Disease, Ministry of Health and Welfare of Japan, recommends IVGG therapy at a dose of 200 mg/kg daily for 5 consecutive days [16]. Groups P_1 and P_2 received the same course of acetylsalicylic acid and IVGG as groups G_1 and G_2 and in addition, oral PTX (Trental, Hoechst Japan, Tokyo) at a dosage of 10 mg/kg per day (P_1) and 20 mg/kg per day (P_2), in three divided doses until the 30th day. Laboratory testing was performed at the time of enrollment and then 1, 2, and 4 weeks thereafter. Blood samples were obtained for a complete blood count, differential white cell count, platelet count, and measurements of albumin, and C-reactive protein. All adverse reactions were noted.

Assessment of CAL

We assessed the presence of CAL by two-dimensional echocardiography. Two-dimensional echocardiography was done prior to treatment and then twice a week after hospital admission. Each study included views of the right coronary artery and of the left main trunk, anterior descending, and circumflex branches of the left coronary artery, as well as of the posterior descending coronary artery. A coronary artery was defined as abnormal if the lumen diameter (inside to inside) was at least 3 mm in a child less than 5 years of age or at least 4 mm in a child 5 years of age or older; if the internal diameter of a segment was at least 1.5 times as large as that of an adjacent segment; or if the lumen was clearly irregular [15].

Statistical analysis

We compared mean values for base-line demographic, and laboratory data and duration of fever at enrollment with two-sample *t*-tests. We investigated the relation of the post-treatment laboratory data between two treatment groups by two-sample *t*-tests. We used chi-square tests to compare the crude prevalence of CAL during a 30-day period after disease onset.

Results

Comparability of treatment groups

At enrollment, the patients in the two treatment groups in study-1 and study-2 had similar demographic characteristics (Table 1) and laboratory data (Table 2).

Table 1 Demographic data at enrollment

Variable	Study-1		Study-2	
	Group G_1	Group P_1	Group G_2	Group P_2
n	18	18	21	22
Sex (M/F)	10/8	9/9	12/9	12/10
Age (months)	24.5 ± 20	30.4 ± 24.4	30.5 ± 19.8	23.8 ± 22.3
Days from onset of fever	4.8 ± 1.3	4.7 ± 2.0	4.6 ± 2.0	4.5 ± 1.6

Values are expressed as mean ± SD

Table 2 Laboratory data at enrollment

Variable	Study-1		Study-2	
	Group G_1	Group P_1	Group G_2	Group P_2
White-cell count ($\times 10^{-9}$/l)	13.4 ± 2.8	15.6 ± 4.8	13.9 ± 6.6	18.0 ± 8.0
Platelet count ($\times 10^{-9}$/l)	345.7 ± 93.9	384.2 ± 116.6	342.8 ± 101.2	375.6 ± 115.4
Albumin (g/l)	38.6 ± 4.0	38.3 ± 4.7	36.2 ± 4.4	39.0 ± 5.3
C-reactive protein (mg/dl)	12.7 ± 6.4	11.3 ± 6.2	11.1 ± 7.0	11.1 ± 4.8

Values are expressed as mean ± SD

Table 3 Total duration of fever and laboratory data on study after 1, 2 and 4 weeks, according to treatment

Variable	Study-1		Study-2	
	Group G_1	Group P_1	Group G_2	Group P_2
Total duration of fever (days)	8.8 ± 3.9	8.9 ± 5.2	9.5 ± 4.6	7.5 ± 2.8
White-cell count ($\times 10^{-9}$/l)				
Week 1	9.7 ± 4.5	10.6 ± 5.4	11.5 ± 6.0	10.5 ± 5.8
Week 2	8.5 ± 2.5	8.5 ± 4.0	8.8 ± 2.6	8.9 ± 2.8
Week 4	7.6 ± 1.5	8.4 ± 2.0	8.1 ± 2.6	9.0 ± 2.9
Platelet count ($\times 10^{-9}$/l)				
Week 1	606.2 ± 194.3	587.4 ± 200.9	544.8 ± 178.3	583.4 ± 232.4
Week 2	514.6 ± 121.6	613.8 ± 194.1	620.8 ± 226.0	525.4 ± 159.7
Week 4	404.8 ± 172.2	447.8 ± 143.5	496.8 ± 218.3	451.1 ± 131.9
Albumin (g/l)				
Week 1	38.6 ± 6.9	38.4 ± 8.5	34.6 ± 5.8	34.9 ± 12.7
Week 2	40.3 ± 3.5	38.0 ± 7.5	39.1 ± 4.7	43.7 ± 6.2
Week 4	45.5 ± 4.6	44.6 ± 3.2	46.4 ± 7.1	44.6 ± 6.0
C-reactive protein (mg/dl)				
Week 1	4.2 ± 6.7	5.7 ± 8.4	5.1 ± 7.6	2.8 ± 3.8
Week 2	2.2 ± 4.6	0.6 ± 1.0	2.2 ± 4.6	1.3 ± 3.4
Week 4	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.2	0.1 ± 0.1

Values are expressed as mean ± SD

Table 4 Clinical features of patients with CAL (*LMT* left main trunk, *LAD* left anterior descending · *RCA* right coronary artery)

		Number of patients with CAL (%)	Case	Age (years)	Sex	Study day from onset when first detected (days)	Aneurysm location	Maximum diameter of coronary artery (mm)
Study-1	Group G_1	3 (16.7)	1	6.7	M	16	LMT LAD RCA	6.4 6.9 5.9
			2	0.2	M	10	LMT	3
			3	2.3	M	16	LMT	4
	Group P_1	2 (11.1)	4	1.7	M	11	LMT LAD RCA	5.3 7 5
			5	1.7	M	10	LMT LAD RCA	6.6 5.9 5
Study-2	Group G_2	3 (14.3)	6	0.3	M	17	LMT RCA	10 10
			7	2.2	M	16	LMT LAD RCA	6 4 4
			8	0.2	M	14	LMT	4
	Group P_2	0 (0)						

Fever and laboratory data

Table 3 shows total duration of fever and post-treatment laboratory data in study-1 and study-2. In study-1, there were no significant differences in the days of total duration of fever between group G_1 and group P_1. In study-2 group P_2 seemed to have a shorter duration of fever after the beginning of therapy than group G_2, but there was no significant difference between the two groups.

In both studies, there were no significant differences in post-treatment laboratory data between group G and P except for a slightly more rapid normalization of CRP in P_2.

Coronary-artery abnormalities

Table 4 shows clinical features of patients with CAL in study-1 and study-2. In study-1, we detected CAL in 3 of 18 patients in group G_1, as compared with 2 of 18 patients in group P_1 during a 30-day period after disease onset. This difference did not reach statistical significance.

In study-2, we detected CAL in 3 of 21 patients in group G_2, as compared with none of 22 patients in group P_2 ($\chi^2 = 6.4$, $P < 0.02$) during a 30-day period after disease onset.

Adverse effects

No adverse side-effects were observed in 79 patients with KD in study-1 and study-2.

Discussion

We have reported that the increases in peripheral blood CD 14^+ macrophage/moncyte counts, serum levels of TNFα and levels of soluble intercellular adhesion molecule 1 in serum are more evident in KD patients with CAL than those without CAL [3, 5, 6]. We have also reported that activated T-cells are temporarily withdrawn from peripheral circulation during acute KD, and that sequestration of activated T-cells may be a feature of this disease [4, 7, 8]. In our opinion, central to the development of CAL may be the expression of adhesion molecules on vascular endothelial cells, which is induced by TNFα secreted by the increased numbers of activated CD 14^+ macrophages/monocytes circulating during the acute phase of KD. Recently, we measured p60 soluble TNF-R shedding into the circulation in patients with acute KD, all of whom received intravenous IVGG. High amounts of soluble TNF-R are produced in any condition in which the activities of TNFα are increased [2, 17]. Patients with CAL had higher levels of soluble TNF-R than did those without CAL [9]. This suggested that KD patients with a marked activation of TNFα seem to be susceptible to CAL in spite of IVGG therapy.

In March 1991, we began a randomized trial in patients with acute KD to administer PTX, which blocks TNFα prodcution [1, 11, 18, 21]. The mechanism by which PTX decreases TNFα mRNA may involve increased cyclic AMP [20]. As shown in this study, oral administration of high-dose (20 mg/kg per day) PTX combined with intravenous IVGG tended to lower the incidence of CAL and slightly accelerated the resolution of systemic inflammation. Low-dose (10 mg/kg per day) PTX was ineffective.

Despite the small number of patients, we believe that oral administration of high-dose PTX in combination with intravenous IVGG is safe and effective in reducing the prevalence of CAL when administered early in the course of KD.

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