Case Report

Continuous Infusion of Cyclosporin A in Intravenous Immunoglobulin Resistant Kawasaki Disease Patients

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Abstract

Treatment of intravenous immunoglobulin (IVIG) resistant Kawasaki disease (KD) is challenging. Continuous infusion of cyclosporin A (CICyA) was employed for 4 patients with IVIG-resistant KD: these patients had remained febrile or had had recurrence of fever within 24 hours after the initial 2g/kg followed by additional 2g/kg IVIG. Response differed between initial doses of CICyA, 1.5 mg/kg/day vs. 3.0 mg/kg/day. The clinical course of the two patients treated with 1.5 mg/kg/day CICyA suggested that the low serum concentration by gradual increase of CICyA did not improve fever or inflammation. The other two patients treated with 3.0 mg/kg/day CICyA became afebrile within 24 hours after initiation of CICyA. They had a subsequently reduced dose of cyclosporin A (CyA) to maintain its appropriate serum concentration (300-500 ng/ml). No coronary artery lesion was detected one month after the onset of KD. The initial dose of 3 mg/kg/day was effective without major side effects and would be a treatment option for IVIG-resistant KD.
(Key words: coronary lesion; cyclosporine; immunoglobulin resistant; Kawasaki disease)

Introduction

Intravenous immunoglobulin (IVIG) 2g/kg and oral aspirin have been recognized as standard treatment for acute-phase Kawasaki disease (KD); however, 10-15% KD patients do not respond to IVIG[1]. Those who remained febrile or had fever recurrence within 24 hours after the initial 2g/kg IVIG are defined as IVIG-resistant KD patients. These patients had an almost nine-fold increased risk of developing coronary artery lesion (CAL) compared with those with good response[2]. Rapid control of the fever or inflammatory response is important to prevent CAL. Treatments for IVIG-resistant KD include additional IVIG, methylprednisolone pulse (MP) therapy[3], plasma exchange therapy, intravenous infliximab or oral cyclosporine[4), 5)] ; however, all these have some drawbacks.

Cyclosporin A (CyA) treatment has been used for pediatric nephrotic syndrome, juvenile idiopathic arthritis, or bone-marrow transplantation with its standard regimen almost established. It has been used also for IVIG-resistant KD patients and for MP- or infliximab-resistant IVIG-resistant KD patients[6), 7), 8), 9)]. However, no standard regimen, especially its initial doses, for IVIG-resistant KD has been established.

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To determine the appropriate regimen of CICyA in IVIG-resistant KD patients we administered different initial doses of CICyA. We employed intravenous route since CICyA achieves more stable serum CyA concentration than oral route. We started CICyA 1.5mg/kg/day for two patients since one previous report indicated that this dose was effective in KD patients[6]. Then, we used 3.0 mg/kg/day for remaining two patients. The clinical courses of these two groups (1.5 vs. 3.0 mg/kg/day of CICyA) gave us some clinical suggestions.

Case Reports

Laboratory data of 4 patients on admission are shown in Table 1. All 4 patients met full diagnostic criteria of KD at the initial diagnosis, with 6 points being the full mark. We obtained informed consent from the parents in all cases to employ CICyA treatment.

Patient 1

A 5-year-old girl with KD was admitted. At the age of 1 year and 11 months, she had had status convulsivus caused by KD and had been treated with controlled brain hypothermia and MP therapy. This time she was treated with oral aspirin 30mg/kg/day and IVIG 2g/kg on day 5 and 7, but her fever had not subsided. We started CICyA 1.5 mg/kg/day and her fever subsided on the next day. On day 11, CICyA was reduced to 1.25 mg/kg/day but fever with leukocytosis recurred. CICyA was increased to previous dose (1.5 mg/kg/day) and her fever subsided again. On day 19, CICyA was replaced with oral CyA 4.5 mg/kg/day. On day 22, she was discharged and no CAL was noted one month after the onset of KD (Table 2, Figure 1).

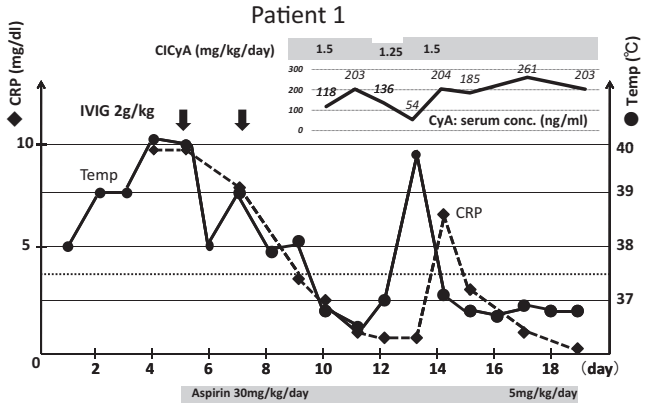

Fig. 1: Clinical course of patient 1. Closed diamond represents serum levels of CRP, and closed circle represents body temperature.
CICyA: continuous infusion of Cyclosporine A, IVIG: intravenous immunoglobulin.

Patient 2

A 1-year-old boy with KD was transferred to our hospital on 7th day after onset of KD because his fever was persistent in spite of IVIG 2g/kg on day 3 and 7. On day 8, his fever had not subsided, and echocardiography revealed poor left ventricle (LV) systolic function (ejection fraction: 52%). Brain

natriuretic peptide concentration had increased to 951 ng/ml. We started CICyA 1.5 mg/kg/day. His fever persisted and CICyA was increased to 2.4 mg/kg/day. On day 17, his fever subsided and the serum concentration of CyA increased to 282 ng/ml. On day 28, CICyA was replaced with oral CyA 6 mg/kg/day. On day 33, he was discharged. Echocardiography revealed transient coronary artery dilatation on day 15 (right coronary artery 3.8mm, left main trunk 3.0mm); however, no coronary artery lesion and normal LV systolic function were noted one month after the onset of KD (Table 2, Figure 2).

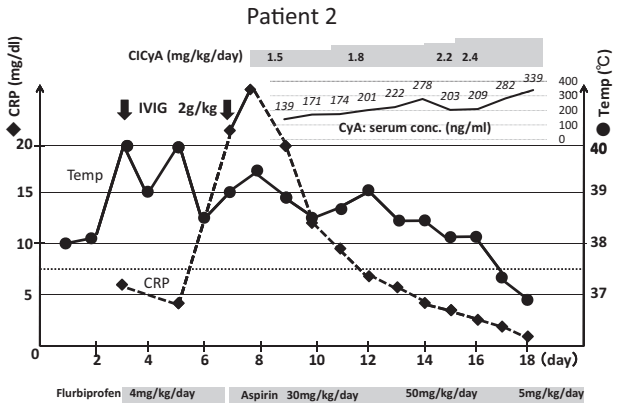

Fig. 2: Clinical course of patient 2

Patient 3

A 2-year-old boy with KD was admitted to another hospital. At the age of 11 months he had had KD and had been treated with IVIG 2g/kg; no CAL had been noted. This time he was treated with IVIG 2g/kg on day 5. On day 7, he was transferred to our hospital and treated with oral aspirin 30 mg/kg/day and additional IVIG 2g/kg. We started CICyA 3.0 mg/kg/day and his fever subsided on the next day, so CICyA was reduced to 2.2 mg/kg/day. On day 12, since mild recurrence of fever was observed, CICyA was increased to 2.6 mg/kg/day. On day 15, his fever subsided again and CICyA was replaced with oral CyA 6 mg/kg/day. On day 23, he was discharged and no CAL was noted one month after the onset of KD (Table 2, Figure 3).

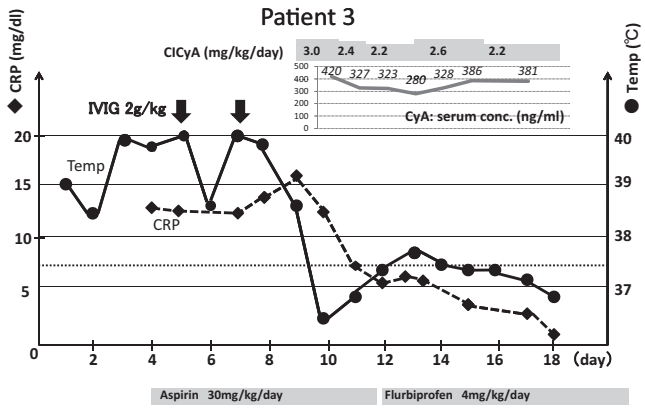

Fig. 3: Clinical course of patient 3

Patient 4

A 9-month-old boy with KD was admitted to another hospital. He was treated with IVIG 2g/kg on day 6 and 8, but his fever had not subsided. On day 9, he was transferred to our hospital. We started CICyA 3.0 mg/kg/day and his fever subsided on the next day. On day 16, since the serum concentration of CyA had increased to 549 ng/ml, CICyA was decreased to 2.3 mg/kg/day. On day 21, CICyA was replaced with oral CyA 6 mg/kg/day. On day 37, he was discharged and no CAL was noted one month after the onset of KD (Table 2, Figure 4).

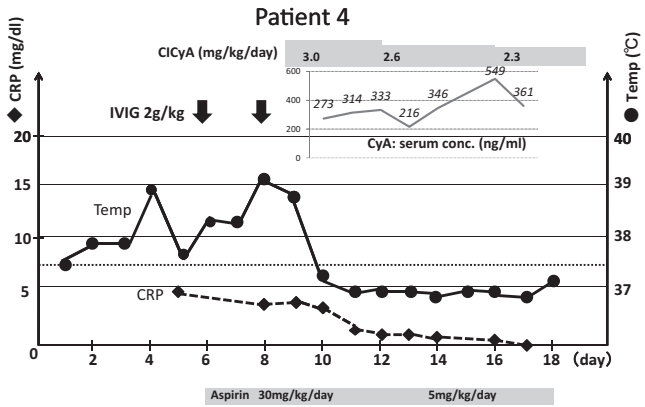

Fig. 4: Clinical course of patient 4

Table 1: Laboratory investigations on admission

Patient	Days of admisson	Diagnostic criteria for KD	Induration at the BCG inoculation site	WBC count ($\times10^4/\mu L$)	neutrophil (%)	Platelet count ($\times10^4/\mu L$)	ESR (mm/h)	CRP (mg/dL)	Serum albumin (g/dL)	AST (mU/mL)	ALT (mU/mL)	Na (mmol/L)	K (mmol/L)	Cr (mg/dL)	Chest X-ray (cardiac size, lung field)	ECG
1	5	6	(-)	19 300	93	27.3	88	9.9	3.2	48	31	132	4.0	0.36	normal	normal
2	7	6	(-)	22 900	89	30.0	101	23.4	2.2	42	32	136	4.3	0.22	CTR 56%	normal
3	7	6	(-)	14 300	77	49.0	128	12.6	2.3	89	64	133	4.9	0.23	CTR 56%	normal
4	9	6	(+)	19 800	49	48.0	138	3.4	3.0	58	31	132	4.7	0.22	normal	normal

CTR: cardiothoracic ratio, ECG electrocardiogram, ESR erythrocyte sedimentation rate

Table 2: Clinical and Laboratory findings associated with CICyA

Patient	Age at Onset	Gender	Initiation of CICyA (days from onset)	Initial dose of CICyA (mg/kg/day)	Duration of fever after CICyA	CyA conc.: 24h after CICyA (ng/ml)	CyA conc.: at the decline of fever (ng/ml)	Duration of CICyA (day)	CAL: 1 month afer oneset	sIL-2R (pre-CICyA) (U/ml)	sIL-2R (3-5 days after CICyA) (U/ml)	Maximum serum K level (mEq/L)
1	5y7m	F	9	1.5	<24h	203	203	10	CAL (-)	777	516	4.5
2	0y4m	M	8	1.5	8 days	139	174	20	CAL (-)	4970	2200	4.8
3	2y6m	M	9	3.0	<24h	420	420	16	CAL (-)	1580	1300	5.4
4	0y9m	M	9	3.0	<24h	273	273	20	CAL (-)	1450	858	5.1

CAL: coronary artery lesion, CyA: cyclosporine A, CICyA: continuous infusion of CyA, sIL-2R: soluble interleukin−2 receptor

Discussion

Treatment for IVIG-resistant KD has not been established and has some drawbacks. For example, MP therapy did not reduce CAL[3] and additional IVIG was associated with blood hyperviscosity. Infliximab cannot be used for patients with tuberculosis or heart failure. Plasma exchange increases the risk of transfusion-transmitted disease and can be performed only at large center hospitals.

We employed CICyA to treat IVIG-resistant KD patients. Oral CyA treatment may be also available; however, oral erosion or unstable absorption in acute KD patients prohibits achievement of stable and sufficient serum CyA concentration. CICyA is a better choice from this viewpoint.

To identify the initial dose and appropriate concentration of CICyA for patients with IVIG-resistant KD, we preliminarily started 1.5 mg/kg/day CICyA in two patients. The first patient had fever recurrence when the serum concentration of CyA decreased to 54 ng/ml. In the second patient, CICyA was gradually increased to 2.4 mg/kg/day, and his fever subsided when his serum concentration of CyA reached 282 mg/ml. These findings suggest that the low serum concentration by gradual increase of CICyA could not improve fever or inflammation in the early phase of the disease. A high serum CyA concentration may be mandatory for rapid reduction of fever and inflammation. Then, we started 3.0 mg/kg/day CICyA in the other two patients within 9 days of illness, which ameliorated fever within 24 hours. CICyA was decreased to maintain adequate serum concentration of CyA (300-500ng/ml) without any fever recurrence.

To prevent the development of CAL in acute KD, maintaining an adequate serum concentration of CyA is required in the initial disease phase, i.e., within the first 10 days, or, if possible, within 7 days of illness[1]. Therefore, we recommend a starting dose of 3mg/kg/day CICyA and to reduce the dose (approximately 2.5 mg/kg/day) to maintain appropriate serum concentration of CyA. CyA clearance in children is greater than in adults, which makes it difficult to maintain an adequate concentration of CyA, and thus frequent monitoring for its serum concentration is needed.

It is unclear whether 3 mg/kg/day CICyA regimen reduced the later occurrence of CAL. Although no CAL was detected one month after onset in patients with an initial dose of 3 mg/kg/day CICyA, a small number of the present patients prohibited us to deduce any conclusion regarding the cardiac outcome. However, rapid control of the fever or inflammatory response by CICyA treatment would improve the cardiac outcome since IVIG-resistant KD patients had increased risk of developing CAL compared with those who responded to initial IVIG (12.2 vs 1.4%)[2]. A prospective study is needed with a large number of patients to confirm the effectiveness of this CICyA regimen.

One of the most major side effects of CICyA is a high serum level of potassium[10]. However, the maximum K level was 5.4 mmol/L in our patients, and no patient developed hypertension or renal dysfunction during or after CICyA.

The present observation may indicate the close association between KD and T-cell activation. CyA prevents dephosphorylation of the nuclear factor of activated T-cells (NF-AT) by binding to cyclophilin, inhibits the production of interleukin-2 and related cytokines in T-cells, and reduces T-cell activation[4]. In our 4 patients after CICyA, fever subsided, CRP fell and soluble interleukin-2 receptor decreased (Table 2).

We have described 4 patients with IVIG-resistant KD in whom two starting regimens of CICyA, 1.5 vs. 3.0 mg/kg/day, were employed. Starting with 3.0 mg/kg/day CICyA followed by a reduction to the

appropriate doses may be effective and safe. Further studies are needed to confirm our supposition.

Declaration of interest: We declare no conflicts of interest. The authors alone are responsible for writing the paper and its contents.

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川崎病のガンマグロブリン不応例に対するシクロスポリン持続静注療法

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要　約

川崎病に対するガンマグロブリン大量静注療法（IVIG）を初回2g/kg で施行したが解熱せず，2g/kg の追加投与に対しても不応であった４症例に対して，シクロスポリン（CyA）持続静注療法を施行した。CyA を1.5mg/kg/day で開始した２例は，血中 CyA 濃度は低く，解熱が遅く，再発熱を認めた。3.0mg/kg/day で開始した２例は，24時間以内に解熱し，有効血中濃度は，300-500ng/ml と示唆された。４例とも発症１ヶ月の時点で冠動脈病変を認めず，重篤な副作用もなかった。以上から，CyA 持続静注療法（開始量3.0mg/kg/day）は，IVIG 不応の川崎病患者に対する治療の選択肢の１つと考えられた。

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