Ulinastatin, a Urinary Trypsin Inhibitor, for the Initial Treatment of Patients With Kawasaki Disease: A Retrospective Study

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Background—Markedly activated neutrophils or higher plasma levels of neutrophil elastase are involved in the poor response to intravenous immunoglobulin (IVIG) and the formation of coronary artery lesions (CAL) in patients with acute Kawasaki disease. We hypothesized that ulinastatin (UTI), by both direct and indirect suppression of neutrophils, would reduce the occurrence of CAL.

Methods and Results—We retrospectively analyzed the clinical records of patients with Kawasaki disease between 1998 and 2009. Three hundred sixty-nine patients were treated with a combination of UTI, aspirin, and IVIG as an initial treatment (UTI group), and 1178 were treated with a conventional initial treatment, and IVIG with aspirin (control group). The baseline characteristics did not demonstrate notable differences between the two groups. The occurrence of CAL was significantly lower in the UTI group than in the control group (3% versus 7%; crude odds ratio [OR], 0.46; 95% confidence interval [CI], 0.25–0.86; \( P=0.01 \)). The OR adjusted for sex, Gunma score (the predictive score for IVIG unresponsiveness), and dosage of initial IVIG (1 or 2 g/kg) was 0.32 (95% CI, 0.17–0.60; \( P<0.001 \)). In addition, most CAL occurred in patients requiring additional rescue treatment and the proportion of those patients was significantly lower in the UTI group than in the control group (13% versus 22%; crude OR, 0.52; 95% CI, 0.38–0.73; \( P<0.001 \)). The adjusted OR was 0.30 (95% CI, 0.20–0.44; \( P<0.001 \)).

Conclusions—UTI was associated with fewer patients requiring additional rescue treatment and reduction of CAL in this retrospective study. (Circulation. 2011;124:00-00.)

Key Words: coronary artery disease ■ Kawasaki disease ■ neutrophils ■ trypsin inhibitors ■ ulinastatin

Kawasaki disease (KD) is an acute febrile illness in children and is pathologically characterized by systemic vasculitis.1 High-dose intravenous immunoglobulin (IVIG), together with aspirin, is clearly effective in resolving inflammation associated with KD and reducing the occurrence of coronary artery lesions (CAL).2,3 However, CAL, including transient dilatation, occurs in >10% of patients despite this therapy.4 The limited efficacy of IVIG therapy has led researchers to seek additional agents in the treatment of KD.

Clinical Perspective on p ●●●

Ulinastatin (UTI), a urinary trypsin inhibitor that protects tissues and organs against neutrophil-mediated injury, is considered to be a reasonable treatment of KD because several investigations have demonstrated that markedly activated neutrophils or higher plasma levels of neutrophil elastase are involved in the poor response to IVIG and the formation of CAL.5–10 For the treatment of KD, UTI has been used since the first clinical report by Okada et al was published.11 However, no sufficient results have been reported confirming the clinical usefulness of UTI in the treatment of KD, although investigators have reported some restrictive efficacies for the patients with KD.11–13

In the present study, we performed an initial treatment with a combination of UTI, aspirin, and IVIG for patients with acute KD. The aim of the present study was to investigate whether UTI in the initial treatment phase improves the coronary artery outcomes for patients with acute KD.
Methods

Patient Population and Data Collection
We retrospectively reviewed the clinical records of patients with KD treated between October 1998 and December 2009 at 14 hospitals in the Saitama and Gunma prefectures in Japan. At the laboratory of National Defense Medical College (NDMC), UTI has been examined for its inhibition of neutrophil-mediated injury in KD, septic shock, and circulatory shock.14–16 On the basis of these experimental results and the clinical reports, we added UTI to the regimen of initial treatment for patients with KD at NDMC.11–13 All patients admitted to NDMC were provided information about UTI, and all patients who provided their informed consent underwent initial treatment with a combination of UTI, aspirin, and IVIG. However, the regimen used in the remaining 13 hospitals did not include UTI either as an initial treatment or as an additional rescue treatment for patients refractory to initial treatment. Patients in those hospitals were treated with a standard, conventional initial treatment, a combination of aspirin and IVIG. We defined patients treated with UTI as the UTI group and patients treated without UTI as the control group and compared the occurrence of CAL between the groups. The present study was approved by the institutional review board at the NDMC.

Diagnosis
Our criteria for a diagnosis of KD included fever (temperature >38°C) accompanied by the presence of at least 4 of the following 5 findings: bilateral conjunctival injection, changes in the lips and the oral cavity, nonpurulent cervical lymphadenopathy, polymorphous exanthema, and changes in the extremities. These diagnostic criteria are compliant with the Diagnostic Guidelines for Kawasaki Disease (5th revision).17 The first day of illness was defined as the first day fever was present.

Patients were excluded if the clinical or laboratory evidence suggested atypical KD or any other disease known to mimic KD, such as adenovirus infection, Epstein-Barr virus infection, scarlet fever, or bacterial cervical lymphadenitis. Patients who presented with CAL before the initial treatment began were also excluded from the study.

Definition of Coronary Artery Lesions
Pediatricians had recurrently assessed the coronary arteries using 2-dimensional echography, and we reviewed their records at least 1 month after the onset of KD. In accordance with the Japanese Ministry of Health criteria, CAL was diagnosed when any of the examinations resulted in the following findings: an internal lumen diameter >3.0 mm in a child <5 years of age or >4.0 mm in a child ≥5 years of age, an internal segment diameter at least 1.5 times larger than that of an adjacent segment, or an irregular lumen.

Comparison of the Coronary Artery Outcomes
We compared the occurrence of CAL between the UTI group and the control group. In addition, we divided the groups into patients at high and low risk of CAL according to the Gunma score, then compared the occurrence of CAL between the UTI group and the control group. The Gunma score is the scoring system developed to predict the risk of CAL.9 This risk score, developed based on a large sample (750 clinical records) and validated during the development process, consists of the following 7 variables (the range of the risk score is 0–11 points): serum sodium, aspartate aminotransferase (AST), percentage of the white cells that represent neutrophils, platelets, C-reactive protein (CRP), age in months, and the days of illness at initial treatment. Patients with a higher score are at a higher risk of IVIG unresponsiveness and CAL formation; moreover, the occurrence of CAL rises sharply at 7 points (the occurrence of CAL at 7 points is 3–5 times higher than that at 6 points).9 Therefore, to identify the patients at high risk of CAL with extremely high specificity, we defined the patients with a Gunma score between 7 and 11 points as those at high risk of CAL in the present study. When we set the cutoff point at 7 points, sensitivity and specificity for prediction of CAL formation were 55% and 92%, whereas the original setting (cutoff point at 4) demonstrated 91% and 60%, respectively.9

Requirements for Additional Rescue Treatment
Additional rescue treatment was provided when patients had persistent fever lasting >24 hours after the completion of the initial treatment or in the presence of recurvedent fever associated with KD symptoms after an afibrile period. We divided the patients who required no additional rescue treatment into the Add Tx (–) subgroup and those who required additional rescue treatment into the Add Tx (+) subgroup. The proportion of the subgroups was then assessed both in the UTI group and in the control group. In addition, the occurrence of CAL was calculated in each subgroup.

Assessment of Adverse Events
Adverse events associated with UTI, such as the elevation of transaminase, neutropenia, rash, and anaphylactic shock (rarely), were reported. In the present study, neutropenia was diagnosed when the neutrophil count decreased to <1500 cells/mm³.

Statistical Analysis
Data are presented as the mean ± SD for continuous variables or as a percentage for categorical variables. Baseline characteristics and components of treatment were compared between the UTI group and the control group using an unpaired t test for continuous variables and Fisher’s exact test for categorical variables. Considering that the use of UTI was completely determined by institutions in the present study, we performed multiple logistic regression analysis to examine the relationship between the use of UTI and the occurrence of CAL. The contribution of UTI to the requirement of additional rescue treatment was also examined by multiple logistic regression. Models were adjusted for sex, Gunma score, and the dosage of initial IVIG (1 or 2 g/kg). Statistical analyses were also

Table 1. Baseline Characteristics of Study Patients

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>UTI Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=1178)</td>
<td>(n=369)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>659 (56)</td>
<td>216 (59)</td>
<td>0.40*</td>
</tr>
<tr>
<td>Age at onset, months</td>
<td>29.8±22.6</td>
<td>29.4±24.7</td>
<td>0.80</td>
</tr>
<tr>
<td>White blood cell count, $\times 10^3$/mm³</td>
<td>15.0±5.0</td>
<td>14.4±4.9</td>
<td>0.06</td>
</tr>
<tr>
<td>Neutrophils, %</td>
<td>68.6±15.1</td>
<td>73.5±12.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Platelet count, $\times 10^9$/mm³</td>
<td>34.7±10.7</td>
<td>34.4±10.5</td>
<td>0.57</td>
</tr>
<tr>
<td>AST, IU/L</td>
<td>110.6±208.7</td>
<td>131.7±272.2</td>
<td>0.17</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>134.5±2.9</td>
<td>134.1±3.2</td>
<td>0.01</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>3.9±0.4</td>
<td>4.0±0.4</td>
<td>0.43</td>
</tr>
<tr>
<td>CRP, mg/dL</td>
<td>8.5±5.2</td>
<td>8.9±5.7</td>
<td>0.22</td>
</tr>
<tr>
<td>Days of illness at initial treatment, days</td>
<td>4.8±1.4</td>
<td>4.7±1.5</td>
<td>0.32</td>
</tr>
<tr>
<td>Gunma score, points</td>
<td>3.5±2.4</td>
<td>4.1±2.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gunma score 0 to 6 points, n (%)</td>
<td>1037 (88)</td>
<td>300 (81)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Gunma score 7 to 11 points, n (%)</td>
<td>141 (12)</td>
<td>69 (19)</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as the mean±SD for continuous variables, as the number of patients (%) for categorical variables. P values were obtained using an unpaired t test, or *using Fisher’s exact text.
Table 2. Components of Treatment

<table>
<thead>
<tr>
<th>Dosage of initial IVIG</th>
<th>Control Group (n=1178)</th>
<th>UTI Group (n=369)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 g/kg</td>
<td>1076 (91)</td>
<td>325 (88)</td>
<td>0.07</td>
</tr>
<tr>
<td>1 g/kg</td>
<td>102 (9)</td>
<td>44 (12)</td>
<td></td>
</tr>
<tr>
<td>Patients who required additional treatment</td>
<td>262 (22)</td>
<td>48 (13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Additional IVIG</td>
<td>219/262 (84)*</td>
<td>46/48 (86)*</td>
<td>NA</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>195/262 (74)*</td>
<td>25/48 (52)*</td>
<td>NA</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>2/262 (0.8)*</td>
<td>0/48 (0)*</td>
<td>NA</td>
</tr>
<tr>
<td>Increase in dosage of UTI†</td>
<td>0/262 (0)*</td>
<td>48/48 (100)*</td>
<td>NA</td>
</tr>
</tbody>
</table>

IVIG indicates intravenous immunoglobulin; UTI, ulinastatin. NA indicates not applicable. Data are presented as the number of patients (%), or as the proportion of the patients that received each additional treatment to all patients that required additional rescue treatment (%).

†The dosage of UTI was increased to twice the original dosage per day. P values were obtained using Fisher’s exact text.

performed for the patient groups at high and low risk of CAL. In addition, after limiting the study period to 2002 to 2009 in order to exclude the patients treated with 1 g/kg initial IVIG, we conducted sensitivity analysis on a subset of the data. Missing data for all variables were not imputed and were treated as missing. To ensure consistency of results, we also performed a multiple imputation analysis (5 repeated imputations were used in the analyses). For all analyses, a 2-sided probability value <0.05 was considered indicative of statistical significance. All statistical analyses were performed with SAS version 9.2 (SAS Institute Inc, Cary, NC).

**Results**

**Characteristics and Laboratory Findings of the Patients**

Three hundred sixty-nine patients in the UTI group and 1178 patients in the control group were included in the present study. Table 1 describes the baseline characteristics and laboratory findings for the UTI group and the control group. No significant differences were found between the UTI group and the control group, with the exception of the percentage of neutrophils, serum sodium level, and the Gunma score. The proportion of patients in the UTI group with a Gunma score between 7 and 11 points was significantly higher than that found in the control group.

**Components of Treatment**

In both the UTI group and the control group, all patients were treated with a combination of aspirin (30 mg · kg⁻¹ · d⁻¹) and high-dose IVIG (1 or 2 g/kg) for the initial treatment. The dosage of aspirin was decreased to 5 mg · kg⁻¹ · d⁻¹ after normalization of the CRP level. In addition, patients in the UTI group received UTI (Miracrid, Mochida Pharmaceutical, Tokyo, Japan) by intravenous infusion (15 000 U · kg⁻¹ · d⁻¹ in 3 divided doses) as part of the initial treatment. UTI was administered until normalization of the CRP level. As shown in Table 2, the proportion of patients receiving 1 g/kg initial IVIG was not significantly different between the UTI group and the control group.

In both the UTI and the control group, all patients that did not respond to the initial treatment, with the exception of 2, were treated with additional IVIG (1 or 2 g/kg) and/or corticosteroids (2 mg · kg⁻¹ · d⁻¹ by intravenous infusion) as an additional rescue treatment. The remaining 2 patients, from the control group, were treated with additional IVIG and corticosteroids, then cyclosporine. In the UTI group, the dosage of UTI was also increased to twice the original dosage per day (in 6 divided doses) for all patients who required additional rescue treatment. No patients in the control group received UTI, even as an additional rescue treatment.

**Comparison of the Coronary Artery Outcomes**

As shown in Table 3, the occurrence of CAL in the UTI group was significantly lower than that found in the control group (12 of 369 [3%] versus 80 of 1178 [7%]; crude odds ratio [OR], 0.46; 95% confidence interval [CI], 0.25–0.86; P=0.01). This was particularly the case for the patients with a Gunma score between 7 and 11 points (at high risk of CAL); the occurrence of CAL in the UTI group was markedly lower than that in the control group (5 of 69 [7%] versus 39 of 141 [28%]; crude OR, 0.20; 95% CI, 0.08–0.55; P=0.002). After adjustment for sex, Gunma score, and dosage of initial IVIG, the occurrence of CAL in the UTI group remained significantly lower than that in the control group.

Sensitivity analyses excluding the patients treated with 1 g/kg initial IVIG showed results similar to those prior to exclusion (data not shown). In addition, multiple imputation analysis showed results similar to those in Table 3 (data not shown).

**Requirements for Additional Rescue Treatment**

The Figure shows the proportion of patients that required additional rescue treatment in the UTI group and in the control group. Within each of the patient groups defined by the Gunma score (Figure, A through C), the proportion of patients in the Add Tx (+) subgroup of the UTI group was...
significantly lower than that found in the control group. For patients with a Gunma score between 7 and 11 points, the proportion of patients in the Add Tx (+) subgroup of the UTI group was almost half that of the control group (25 of 69 [36%] versus 95 of 141 [67%]; crude OR, 0.28; 95% CI, 0.15–0.50; \( P < 0.001 \)). After adjustment for sex, Gunma score, and dosage of initial IVIG, the proportion of patients requiring additional rescue treatment in the UTI group remained significantly lower than that in the control group (Figure, A through C).

As shown in Figure, A through C, the occurrences of CAL in the Add Tx (+) subgroup were always markedly higher than those in the Add Tx (−) subgroup both for the UTI group and for the control group.

However, the occurrences of CAL in either the Add Tx (+) subgroup or the Add Tx (−) subgroup were not significantly different between the UTI group and the control group (data not shown). These results were similarly found in each of the patient groups defined by the Gunma score (Figure, A through C).

In addition, the results of sensitivity analyses excluding the patients treated with 1 g/kg initial IVIG were similar to those prior to exclusion (data not shown). Multiple imputation analysis also showed results similar to those in the Figure (data not shown).

Assessment of Adverse Events

No adverse events associated with UTI were observed.

Discussion

The principal findings in the present study are as follows: (1) the occurrence of CAL in the UTI group was significantly lower than that in the control group; (2) for patients at high risk of CAL (a Gunma score between 7 and 11 points), the occurrence of CAL in the UTI group was markedly lower than that in the control group.

To elucidate why the occurrence of CAL in the UTI group was lower than that in the control group, we assessed the requirement for additional rescue treatment in each group. In this analysis, most patients with CAL were included in the subgroup of patients that required additional rescue treatment. This result indicates that success of the initial treatment is crucial for the prevention of CAL; this concurs with several previous reports.\(^9,19–21\) More importantly, this analysis demonstrated that the proportion of patients that required additional rescue treatment was significantly lower in the UTI group than in the control group. Therefore, we speculated that UTI increased the success rate of the initial treatment and increased the number of patients that required no additional rescue treatment, consequently decreasing the occurrence of CAL.

The present study contained two dosages of initial IVIG (1 or 2 g/kg) due to the long study period, as shown in Table 2. However, even when we limited the study period to 2002 to 2009 in order to exclude the patients treated...
with 1 g/kg, the statistical results were similar to those prior to the time limitation. Therefore, we estimate that the use of two doses of initial IVIG had little influence on our conclusions.

In the present study, missing data were not imputed and were treated as missing. Findings for multiple imputation analysis were similar to results without multiple imputation. Based on the consistency of results in these analyses, we considered that bias related to missing values was little. It is unlikely that missing data would significantly change our conclusions.

UTI, clinically used for the treatment of circulatory shock, septic shock, and acute respiratory distress syndrome, has a variety of therapeutic mechanisms: (1) activity inhibition of neutrophil elastase and other proteases; (2) suppression of protease secretion from neutrophils via stabilization of the lysosomal membrane; (3) an inhibitory effect on the production of cytokines and adhesion molecules, such as interleukins 1, 6, and 8, tumor necrosis factor α, intercellular adhesion molecule-1, and endothelial leukocyte adhesion molecule-1; (4) anti-inflammation; and (5) antioxidation. Moreover, UTI may also prevent the development of CAL by reversing the imbalance in favor of matrix metalloproteinase activation because neutrophil elastase activates matrix metalloproteinases and degrades tissue inhibitors of matrix metalloproteinases. However, neutrophils infiltrate in the early stage (7–9 days after onset) and produce neutrophil elastase, various inflammatory cytokines, and superoxide anions, which contribute to the formation of CAL. Thus, the clinical use of UTI may be more beneficial in the initial treatment than in additional rescue treatment. Recently, some pediatricians have focused on effective initial treatments combined with aspirin and IVIG to reduce the occurrence of CAL due to the limited efficacy of additional rescue treatment. We propose that UTI is an effective candidate for intensive initial treatment.

To date, investigations of UTI in the acute phase of KD have demonstrated the inhibitory effect of arachidonic metabolism by inhibiting prostaglandin H2 synthase and the suppression of oxidant stress (NO3−). In addition, the clinical usefulness of UTI for the treatment of KD has been reported. Okada et al demonstrated that UTI short‐ened the febrile period in their retrospective study. Iwashima et al reported that the antipyretic effect of UTI plus IVIG therapy may appear to be greater than that of IVIG alone and that the initial treatment with UTI may reduce the total dosage of IVIG in a subset of patients with KD. In the present study, our results also showed that fewer patients required additional rescue treatment in the UTI group than in the control group. Nevertheless, a decrease in the occurrence of CAL has never been demonstrated except for the present study, possibly because the examinations used small sample sizes to assess the efficacy of UTI. Therefore, the present study is valuable for its large sample size and because it is the first report demonstrating that UTI is associated with a reduction of CAL.

Limitations
Some drawbacks exist in the present study. First, this is a nonrandomized, retrospective study. Because the use of UTI was determined by the institutions and all patients in the UTI group were derived from only 1 institution, there may be unobserved or unmeasured confounders associated with the clinical institutions. All potential bias and confounders cannot be ruled out, although we presented the adjusted ORs of treatment using multivariate analysis.

Second, a standardized protocol for the management of patients, especially patients refractory to initial treatment, was not in place at the participating institutions because of the retrospective nature of the study. Some variations in additional rescue treatments for refractory patients may exist. However, although there were some differences in the components of the additional rescue treatment or in the timing of the decision to add rescue treatment, the occurrences of CAL in the patients who required additional rescue treatment were not significantly different between the UTI group and the control group. The variations in management are unlikely to have had a considerable impact on our conclusions in the present study.

Third, CAL was diagnosed according to Japanese Ministry of Health criteria, which are simple and easy to use in clinical settings. One should note, however, that De Zorzi et al have reported that the use of Japanese Ministry of Health criteria might underestimate the true prevalence of CAL in patients with KD. Fourth, this study excluded patients with atypical KD and those who presented with CAL before the initial treatment began. Our results cannot be generalized to these patients, although physicians may have concern for the management of their care.

Conclusions
Our retrospective study is the first report demonstrating that UTI is associated with fewer patients requiring additional rescue treatment and a reduction of CAL. Further study and a randomized prospective trial are necessary to confirm the clinical benefits of UTI.

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References

CLINICAL PERSPECTIVE

The present study is the first report demonstrating that ulinastatin (UTI), a urinary trypsin inhibitor, is associated with fewer patients requiring additional rescue treatment and reduction of coronary artery lesions in the treatment of Kawasaki disease (KD). UTI, which protects tissues and organs against neutrophil-mediated injury, has been clinically used for the treatment of circulatory shock, septic shock, and acute respiratory distress syndrome. The results of our retrospective study suggested the usefulness of UTI as an initial treatment of KD, although UTI has been used mainly as an additional rescue treatment for patients refractory to initial treatment. Considering the pathological finding of neutrophils in the early stage of KD, clinical use of UTI may be more beneficial in initial treatment than in additional rescue treatment. Moreover, initial treatment with a combination of intravenous immunoglobulin and UTI may reduce not only the occurrence of coronary artery lesions but also the number of patients requiring additional rescue treatment, leading to possible benefits in total cost. No adverse events associated with UTI were observed in the present study. We consider that UTI is an effective candidate for intensive initial treatment to improve the clinical course and coronary outcome among patients with KD. Further study and a randomized prospective trial are needed to confirm the clinical benefits of UTI.
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