Does Abciximab Enhance Regression of Coronary Aneurysms Resulting From Kawasaki Disease?

Richard V. Williams, MD; Venus M. Wilke, MD; Lloyd Y. Tani, MD; and L. LuAnn Minich, MD

ABSTRACT. *Objective.* **Acute Kawasaki disease can result in the development of large coronary artery aneurysms that may persist. Abciximab, a platelet glycoprotein IIb/IIIa receptor inhibitor, is associated with resolution of thrombi and vascular remodeling in adults with acute coronary syndromes. The purpose of this study was to compare changes in aneurysm diameter at early follow-up in patients who had Kawasaki disease and received abciximab in addition to standard therapy with those who were treated with standard therapy alone.**

Methods. **Patients with Kawasaki disease and large aneurysms were divided into 2 groups on the basis of acute therapy: 1) abciximab in addition to standard therapy and 2) standard therapy alone. Echocardiograms were reviewed for coronary aneurysms (lumen diameter 1.5 times that of the adjacent vessel). Maximum aneurysm diameter was determined during the acute/subacute phase of Kawasaki disease (<6 weeks) and at early follow-up (4–6 months). Regression of the aneurysm was defined as a decrease in lumen diameter, and resolution was defined as normalization of the vessel.**

Results. **Six patients had 20 aneurysms in the abciximab group, and 9 patients had 30 aneurysms in the standard therapy group. Early follow-up data were available for 19 of the 20 aneurysms in the abciximab group and 19 of the 30 aneurysms in the standard therapy group. Patients who were treated with abciximab demonstrated greater regression in aneurysm size at early follow-up than patients who were treated with standard therapy alone (percentage decrease: 41 ± 19% vs 17 ± 27%). In the abciximab group, 68% (13 of 19) of aneurysms resolved at early follow-up compared with 35% (7 of 19) in the standard therapy group.**

Conclusions. **Patients who were treated with abciximab demonstrated greater regression in aneurysm diameter at early follow-up than patients who received standard therapy alone. These findings suggest that treatment with abciximab may promote vascular remodeling in this population and warrants further study.** *Pediatrics* **2002;109(1). URL: http://www.pediatrics.org/cgi/content/full/109/1/e4;** ***Kawasaki disease, coronary artery abnormalities, abciximab.***

Kawasaki disease is an acute generalized vasculitis of unknown cause that affects primarily infants and young children. The most significant abnormality that results from acute Kawasaki disease is the development of coronary artery changes. Therapy during the acute phase of the illness is directed toward reducing inflammation and preventing clot formation in an effort to prevent short- and long-term complications related to coronary artery changes. The American Heart Association currently recommends treatment with a single, high dose of intravenous γ globulin and high-dose aspirin during the acute phase of the illness.[1] This treatment regimen has reduced the incidence of coronary artery aneurysms and ectasia from 20% to approximately 5%.[1,2] In addition to the 5% general risk, a subset of patients at each end of the age spectrum—that is, <6 months or >8 years of age—are more likely to have an atypical presentation with a delay in diagnosis and have a higher incidence of coronary artery changes at presentation.[3–6]

Patients who develop large coronary artery aneurysms have the greatest tendency to form thrombi within these aneurysms and have persistence of their vascular abnormalities despite receiving what is currently considered appropriate treatment. This subgroup of patients may benefit from new pharmacologic agents that are more specifically directed toward endothelial abnormalities. Abciximab is a glycoprotein IIb/IIIa receptor inhibitor that has been shown to prevent thrombotic complications and promote vascular remodeling in adults with acute coronary artery syndromes.[7] Although drugs that affect the glycoprotein IIb/IIIa receptor pathway have been used for thrombolysis in Kawasaki disease,[8,9] their effect on vascular remodeling has not been reported. After rapid regression of large coronary artery aneurysms was noted in a patient after use of abciximab for thrombolysis at our institution,[8] we began using this agent as part of initial therapy in patients who have acute Kawasaki disease and present with large aneurysms with or without evidence of intracoronary thrombus. The purpose of this study was to compare changes in the diameter of coronary artery aneurysms in patients who had Kawasaki disease and received abciximab in addition to standard therapy, as recommended by the American Heart Association, with the changes seen in those who received standard therapy alone.

METHODS

Study Population

The Primary Children's Medical Center cardiology database was searched to identify all patients who had coronary artery abnormalities resulting from Kawasaki disease and were seen between 1986 and 2000. Only patients with at least 1 large coronary artery aneurysm (diameter ≥5 mm), with or without throm-

From the Division of Cardiology, Department of Pediatrics, Primary Children's Medical Center, and the University of Utah, Salt Lake City, Utah.
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Reprint requests to (R.V.W.) Primary Children's Medical Center, 100 N. Medical Dr, Ste 1500, Salt Lake City, UT 84113. E-mail: pcrwilli@ihc.com

TABLE 1. Demographics Data for Patients Who Were Treated With Abciximab (Group 1) and Those Who Received Standard Therapy (Group 2)*

Patient	Age (Mo)	Weight (kg)	No. CAA
Group 1			$n = 20$
1	23	15	4
2	4	6.8	3
3	23	11.1	4
4	5	8.1	4
5	7	8	4
6	2	5.1	1
Mean ± SD	11 ± 10	9.0 ± 3.6	
Group 2			$n = 30$
1	4	5.8	3
2	5	8.1	4
3	7	7.8	4
4	7	8.5	4
5	84	32	3
6	10	8.2	3
7	4	5.1	3
8	42	12.2	3
9	78	17.7	3
Mean ± SD	27 ± 33	11.7 ± 8.5	

* There was no significant difference in age or weight between the 2 groups. CAA indicates coronary artery aneurysm.

bus, were included. Data from our institution suggest that aneurysms ≥5 mm in diameter are likely to persist.[10] Medical records were reviewed for age, weight, presenting symptoms, treatment regimen, and bleeding complications.

Treatment Regimens

Patients were divided into 2 groups on the basis of the therapy they received during the acute phase of the illness. Group 1 patients received abciximab in addition to standard therapy (intravenous γ globulin, 2 g/kg as a single dose, in addition to aspirin, 80–100 mg/kg/day). Intravenous γ globulin was given 24 to 48 hours before abciximab in each group 1 patient. Abciximab was administered intravenously as a loading bolus dose of 0.25 mg/kg, followed by an infusion of 0.125 μg/kg/minute for 12 hours. Abciximab dosing was based on the weight-based dose used in adult trials.[11] Group 2 patients received standard therapy alone. In addition, because all patients had large coronary artery aneurysms, patients in both groups were heparinized and subsequently stabilized on warfarin before hospital discharge.

The off-label use and potential bleeding complications associated with abciximab, as well as potential unknown risks in children, were discussed at length with patients' families before administering abciximab, and verbal consent for treatment was obtained in each case. Abciximab was administered in the pediatric intensive care unit with close monitoring of platelet count and coagulation times (prothrombin time and partial thromboplastin time).

Aneurysm Evaluation

Echocardiograms were reviewed and maximal coronary artery aneurysm diameter was measured in the acute phase of the illness (0–6 weeks) and at early follow-up (4–6 months). All echocardiographic views were reviewed, and the largest internal diameter of each coronary artery aneurysm was determined. In 1 patient in the abciximab group, only angiographic data were available at early follow-up; angiograms were reviewed, and the largest internal diameter of each coronary artery aneurysm was used for analysis. For this study, aneurysms were defined as lumen diameter 1.5 times that of the adjacent, normal-caliber vessel. For example, for a 5-mm coronary artery segment to be considered an aneurysm, the adjacent vessel had to be ≤2.5 mm in diameter.

The percentage change in coronary artery size from the acute-phase study to the follow-up study was determined ([initial diameter − follow-up diameter]/initial diameter). For this study, regression was defined as a decrease in lumen diameter at the follow-up study, and the percentage decrease was calculated for each aneurysm. Resolution was defined as the return of the coronary artery diameter to normal.

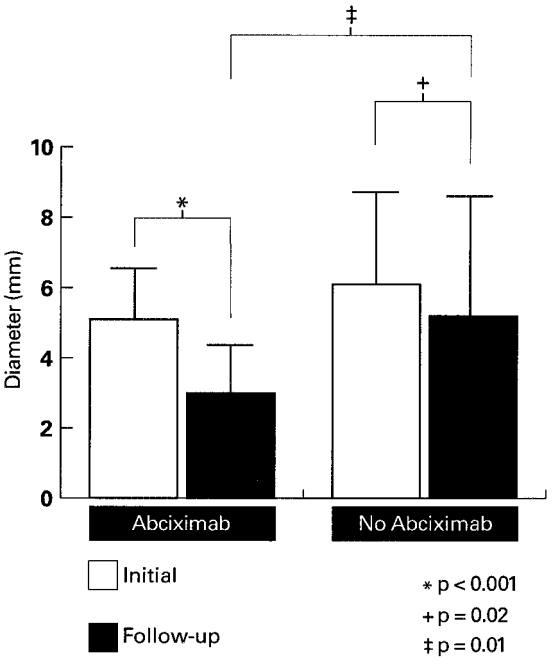

Fig 1. Maximum lumen diameter of aneurysms at baseline and at early follow-up in patients who received abciximab (group 1) and those who did not receive abciximab (group 2). There was a significant decrease in aneurysm size at early follow-up in both groups. The maximum lumen diameter at early follow-up was significantly smaller in the abciximab group.

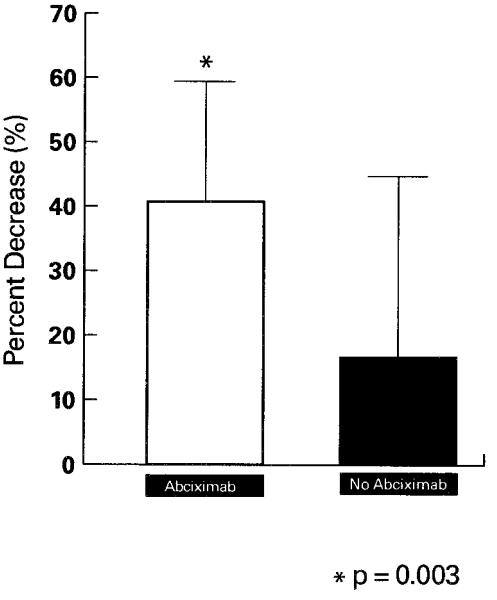

Fig 2. Percentage decrease in aneurysm size in patients who were treated with abciximab (group 1) and those who did not receive abciximab (group 2). Group 1 patients demonstrated a significantly greater percentage decrease in aneurysm lumen diameter than group 2 patients.

Statistical Analysis

Data are expressed as the mean ± standard deviation or percentages. Continuous data between groups were compared using an unpaired Student's t test or Mann-Whitney rank sum test where appropriate. A Wilcoxon signed rank test was used to assess differences within the 2 groups from the acute/subacute study to the early follow-up study. Categorical data were assessed using a χ^2 test. Statistical significance was defined as $P < .05$.

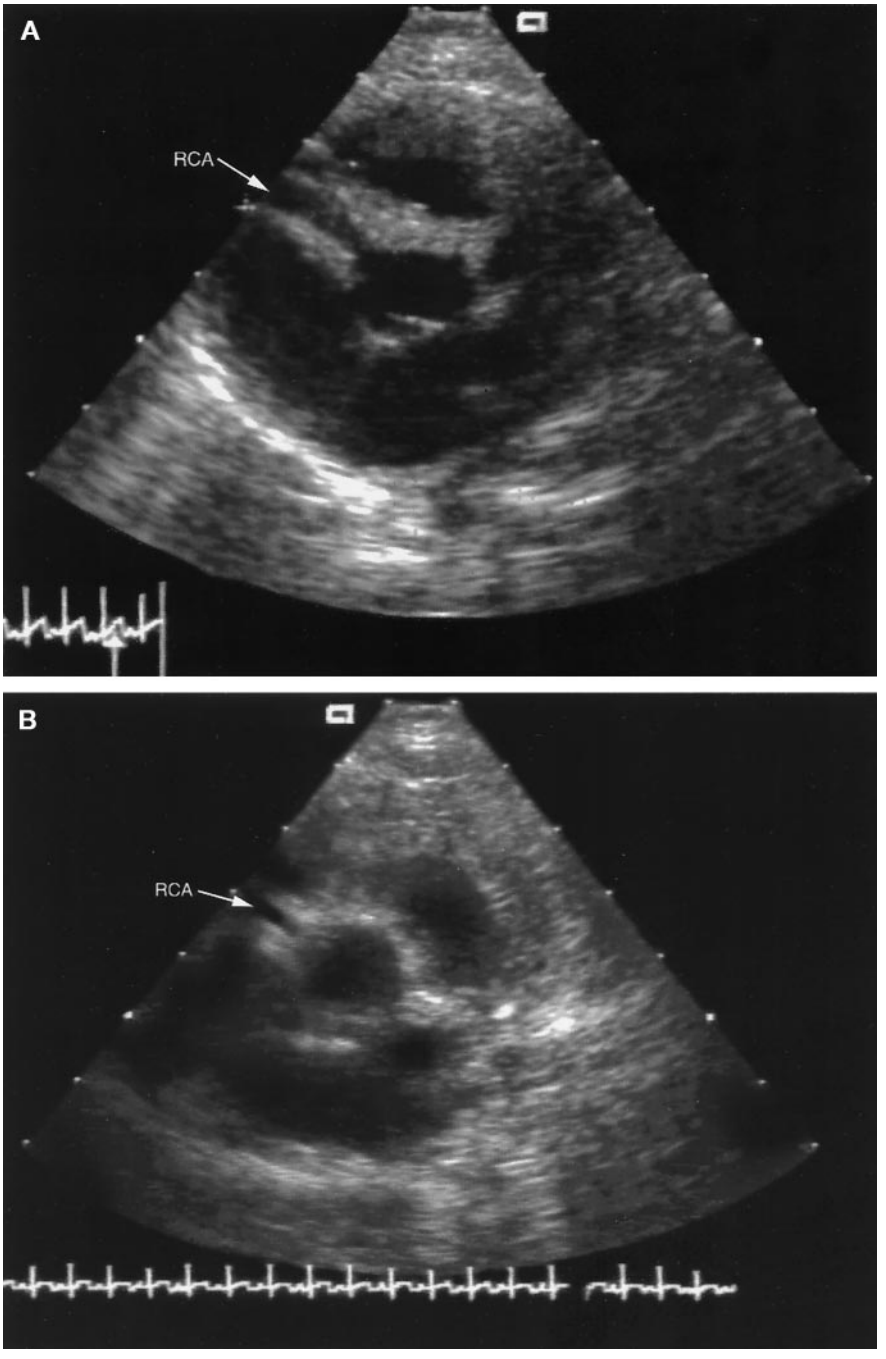

Fig 3. Echocardiographic images of an aneurysm of the right coronary artery from a patient who was treated with abciximab in the acute phase of the illness (A) and at early follow-up (B). Images were obtained from the parasternal short axis imaging plane, and the scale is the same in each image (scale markers are 10 mm). When acute and early follow-up images are compared, there has been a significant decrease in the lumen diameter of the fusiform aneurysm of the proximal right coronary artery. RCA, right coronary artery.

Statistical analysis was performed using SigmaStat software (SPSS, Inc, Chicago, IL).

RESULTS

Patient Data

Fifteen patients were identified for inclusion in this study (Table 1). The 6 patients who received abciximab in addition to standard therapy formed group 1, and the 9 patients who received standard therapy alone formed group 2. There were no significant differences in age or weight between the 2 groups. In group 1, 5 of 6 patients had an atypical presentation, ie, they did not fulfill the complete American Heart Association's diagnostic criteria,[1] and 4 of 9 patients in group 2 had atypical disease. All patients received intravenous γ globulin and high-dose aspirin at the time of diagnosis (standard therapy). In group 1, 5 of the 6 patients had evidence of thrombus within 1 or more aneurysms, and 5 of the 9 patients in group 2 had evidence of thrombus within an aneurysm.

There were no significant bleeding complications (ie, bleeding requiring transfusion) in any of the patients who received abciximab. One patient had a transient episode of lower gastrointestinal tract bleeding after completing the abciximab infusion, which resolved without intervention. No patient in the abciximab group developed unexpected adverse effects during the follow-up period.

Echocardiographic Findings

The 6 patients in group 1 who received abciximab in addition to standard therapy had 20 aneurysms, and the 9 patients in group 2 who received standard therapy alone had 30 aneurysms. At 4- to 6-month follow-up, data were available for 19 of the 20 aneurysms in group 1 and 19 of the 30 in group 2. There was no difference between the 2 groups in aneurysm size at baseline. Although there was a significant decrease in aneurysm size in both groups at early follow-up, the aneurysm diameter was significantly smaller in group 1 when compared with patients in group 2 (3.0 ± 1.3 mm vs 5.2 ± 3.4 mm; $P = .01$; Fig 1). Patients in group 1 also demonstrated a significantly greater percentage decrease in aneurysm size when compared with group 2 ($41 \pm 19\%$ vs $17 \pm 27\%$; $P = .003$; Fig 2). Echocardiographic and angiographic examples of coronary artery aneurysms that regressed from patients in group 1 are shown in Figs 3 and 4. Resolution of coronary artery aneurysms occurred in 68% (13 of 19) of aneurysms in the group treated with abciximab and 37% (7 of 19) of aneurysms in the standard therapy group ($P = .10$).

Data were available for all 20 aneurysms in group 1 and all 30 in group 2 on review of 1- to 5-year follow-up studies. Aneurysm diameter was significantly smaller in group 1 patients when compared with group 2 at the time of the follow-up evaluation (2.7 ± 1.0 vs 4.7 ± 3.1 mm, respectively; $P = .004$). The percentage decrease in aneurysm size was also significantly greater in group 1 ($45 \pm 16\%$ vs $30 \pm 23\%$; $P = .005$).

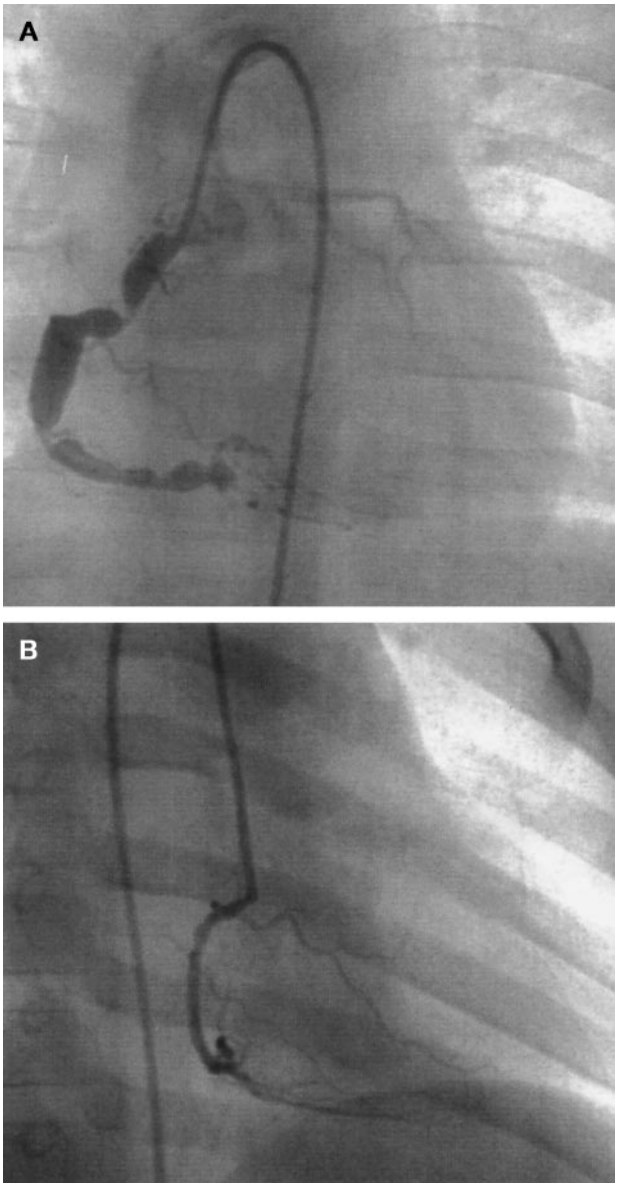

Fig 4. Angiographic images of multiple aneurysms of the right coronary artery in a patient who was treated with abciximab in the acute phase of the illness (A) and at follow-up (B). The significant decrease in aneurysm size can be easily appreciated. These angiograms were obtained using a 4-French catheter (1.3-mm diameter).

DISCUSSION

In this study, patients who were treated with abciximab demonstrated greater regression of coronary artery aneurysms at early follow-up when compared with patients who were treated with standard therapy alone. There was also a trend toward greater aneurysm resolution in the group of patients who were treated with abciximab. Although the standard use of intravenous γ globulin and aspirin has significantly decreased the incidence of coronary artery changes, coronary artery aneurysms have not been entirely eliminated, especially in high-risk groups. Beyond the administration of intravenous γ globulin and aspirin, there is no consensus regarding management of large coronary artery aneurysms. Some centers have used thrombolytics to dissolve clots, only to find frequent recurrence of thrombi within the aneurysm.[12] Regardless of treatment methods, resolution of large coronary artery aneurysms does not seem to occur.[2,10,13,14] In addition, long-term follow-up studies suggest functional coronary artery abnormalities with significantly reduced vasodilating capability despite a relatively normal angiographic appearance of the vessels.[15,16]

Agents that promote vascular remodeling have recently received a great deal of attention in the adult literature.[7,11,17] Abciximab, a human-murine monoclonal antibody fragment that binds to the glycoprotein IIb/IIIa receptor on the platelet surface to prevent platelet aggregation, has been one of the most widely used. Agents that act via the glycoprotein IIb/IIIa receptor pathway have previously been reported to treat thrombi in Kawasaki patients successfully.[8,9] In addition to this property, however, abciximab has other pharmacological properties that may be useful in Kawasaki disease.[7] First, it binds to vitronectin receptors and may impede adhesion of vascular smooth muscle cells to the receptor ligands at the site of vascular inflammation. In addition, by binding to the Mac-1 receptor, the drug may interfere with the recruitment of circulating monocytes to sites of vascular injury. Preliminary investigation suggests that abciximab can impede migration and promote apoptosis of smooth muscle cells, thereby aiding in coronary artery remodeling.[7] If abciximab proves to have these desirable effects on the vasculature, then it may become a useful drug to treat the

endothelial abnormalities associated with Kawasaki disease.

This study has several limitations. First, it is retrospective and the patients who received abciximab were treated in a more recent time period (since 1997). Although patients in both groups received standard therapy as recommended by the American Heart Association, it is possible that patients who were treated during the later period of the study were diagnosed and treated earlier, as physicians became more aware of "atypical" cases. However, analysis of this data in our study is limited because of the small sample size. Second, the results presented here are from a small group of patients. Although the incidence of large coronary artery aneurysms is relatively low, these changes are associated with increased morbidity and mortality, making this an ideal group for a prospective, multicenter, randomized trail. Finally, this study provides only short-term follow-up. Although our available long-term follow-up data suggest the difference between patients who received abciximab in addition to standard therapy and patients who received standard therapy alone persists, the wide range of follow-up intervals makes interpretation of this information difficult. Although the results are promising, prospective, long-term follow-up studies will be necessary to determine whether treatment of patients with Kawasaki disease and large aneurysms with abciximab promotes vascular remodeling and improvement in endothelial function with a reduction in long-term sequelae, including coronary artery stenosis and myocardial infarction.

CONCLUSION

In our small cohort of patients with large coronary artery aneurysms after Kawasaki disease, patients who were treated with abciximab in addition to standard therapy had a significantly greater decrease in the size of their aneurysms when compared with patients who received standard therapy alone. Patients who received abciximab also demonstrated a tendency toward resolution of their coronary abnormalities. Additional studies are needed to evaluate the role of this promising therapy in the treatment of Kawasaki disease.

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