Anti-Human von Willebrand Factor Monoclonal Antibody AJvW-2 Prevents Thrombus Deposition and Neointima Formation After Balloon Injury in Guinea Pigs

Shunsuke Kageyama, Hiroshi Yamamoto, Ryota Yoshimoto

Abstract—Immediately after angioplasty, platelet adhesion to the injured arterial wall and subsequent release of various mitogens may contribute to neointima formation. The purpose of this study was to evaluate the inhibitory effect of AJvW-2, a monoclonal antibody against human von Willebrand factor (vWF), on neointima formation in a guinea pig model. The carotid artery was injured with a balloon catheter, and AJvW-2 was administered by a single bolus injection. AJvW-2 dose-dependently prevented neointima formation 14 days after injury. Significant inhibition was observed at 1.8 mg/kg, at which dose significant inhibition of platelet aggregation was achieved for 2 days. By elastic-Masson staining, organized thrombi were observed in the neointimal lesion on day 14. The thrombus area was significantly correlated with neointimal thickness. Furthermore, thrombus deposition, immunostained for vWF and fibrin(ogen), was observed on the media immediately after balloon injury. AJvW-2 significantly reduced the deposition of both adhesive proteins and reduced the incidence of organized thrombus formation, which might affect subsequent neointima formation. However, the proliferation of cultured smooth muscle cells was not affected by AJvW-2. These results suggest that AJvW-2 prevents neointima formation by inhibition of initial platelet-mediated thrombus formation rather than by direct inhibition of smooth muscle cell proliferation. (Arterioscler Thromb Vasc Biol. 2000;20:2303-2308.)

Key Words: AJvW-2 ■ von Willebrand factor ■ thrombus ■ angioplasty ■ antibodies

Percutaneous transluminal coronary angioplasty (PTCA) is followed by the development of restenosis within 6 months in ≈30% of patients.1–3 Pathophysiologically, restenosis is characterized by several components, such as smooth muscle cells (SMCs), extracellular matrix, and organized thrombus, in the neointimal lesion; however, the precise interplay between these components remains unclear.4–6

Immediately after angioplasty, platelets adhere to the injured vessel wall and release various mitogens, such as platelet-derived growth factor (PDGF), leading to SMC migration, proliferation, and excessive extracellular matrix synthesis. The interaction of von Willebrand factor (vWF) with platelet membrane glycoprotein (GP) Ib plays a crucial role in platelet adhesion to the injured vessel wall7–9 and in the subsequent development of an arterial thrombus.10–12

AJvW-2 is a murine monoclonal antibody against human vWF with a specific inhibitory effect on the GPIb-vWF axis.13 In addition, AJvW-2 cross-reacts well with vWF of other species, and this antibody inhibits thrombus formation in guinea pigs and has a lower bleeding risk than has been observed with the GPIIb/IIIa blockers.13 In addition, thrombus inhibition was more efficient in arterial thrombosis than in venous thrombosis in hamsters, compatible with a shear stress–dependent inhibitory action.14

In the present study, we evaluated the inhibitory effect of AJvW-2 on thrombus deposition onto the vessel wall and the subsequent neointima formation after balloon injury in guinea pigs by investigating the involvement of thrombus generation in neointima formation.

Methods

Study Design
To evaluate neointima formation and thrombus organization, guinea pigs were randomized to either a control group treated with saline (n=13) or with AJvW-2 at doses of 0.6 mg/kg (n=13) or 1.8 mg/kg (n=10). For the immunohistochemical study, guinea pigs were randomized to either a control group (n=20) or to a group treated with AJvW-2 (1.8 mg/kg, n=20) and were euthanized for the preparation of paraffin-embedded cross sections 1, 3, 7, or 14 days (n=5 each in both groups) after angioplasty. All procedures involving the care and use of animals were approved by the Institutional Animal Care and Use Committee of Pharmaceutical Research Laboratories of Ajinomoto Co before they were performed.

Angioplasty
Hartley male guinea pigs, weighing 350 to 550 g, were anesthetized with intraperitoneal sodium pentobarbital (40 mg/kg), and the left common carotid artery was exposed. A 2F Fogarty balloon catheter (Baxter) was inserted through the external carotid artery and advanced into the thoracic aorta. The balloon was inflated and advanced back and forth twice. The catheter was withdrawn, and the external carotid artery was ligated. In the present study, heparin (Novo Nordisk) was intravenously administered to all animals via the ear vein at dose of 100 U/kg 30 minutes before angioplasty. In
addition, either saline or AJvW-2 was administered 20 minutes before angioplasty.

Fourteen days after balloon injury, the animals were anesthetized, and both common carotid arteries were removed, rinsed with saline, and fixed with 10% buffered formalin. Each artery was divided into 2 sections (5-mm length) and vertically embedded in the same paraffin block. Two consecutive cross sections (4-μm thickness) were cut at 1 mm intervals and stained with hematoxylin and eosin for the measurement of neointimal thickness and with elastic-Masson for the measurement of the organized thrombus area.

**Immunohistochemistry**

All procedures were performed according to the labeled streptavidin biotin method. Formalin-fixed paraffin-embedded sections were pretreated with 3% H2O2. After treatment with goat serum (Dako) for 20 minutes, sections were incubated with either rabbit polyclonal antibody for vWF (Dako) or for fibrinogen (Dako) for 1 hour. After 3 washes in PBS, sections were incubated with biotinylated goat anti-rabbit immunoglobulins (Dako) for 20 minutes. A peroxidase-conjugated streptavidin was applied for 10 minutes, and bound peroxidase was detected with diaminobenzidine as a chromogenic substrate. Slides were counterstained with hematoxylin. Antigen retrieval was needed by treatment with 0.1% trypsin for vWF immunostaining. In addition, to avoid nonspecific binding, biotinylated goat anti-rabbit immunoglobulins (Dako) was adsorbed with normal guinea pig plasma at room temperature before usage.

**Quantification**

All quantification was performed with a computerized image graphic analyzer (Mac Scope). The areas of the intima, media, and organized thrombus were measured, and neointimal thickness was expressed as the ratio of intimal to medial area (I/M ratio). Four sections per artery were evaluated, and the highest score of I/M ratio was selected for each animal. The degree of organized thrombus was expressed as the ratio of thrombus (red-stained region with elastic-Masson) to the medial area (Th/M ratio). For the measurement of vWF and fibrinogen deposition, positively stained areas and medial or intimal areas were measured in each segment, and deposition was calculated by the following formula: (vWF- or fibrinogen-positive area)/(medial or intimal area)×100 (%). Two sections per artery were evaluated (n=5 in each group).

**Ex Vivo Platelet Aggregation**

Hartley guinea pigs, weighing 300 to 500 g, were used. Either saline or AJvW-2 (0.6 or 1.8 mg/kg) was intravenously administered via the ear vein (n=4 each). After 5 minutes and at 1, 2, and 3 days, blood was collected from the aorta, anticoagulated with trisodium citrate (0.38% final concentration), and centrifuged at 1100 rpm for 10 minutes to obtain platelet-rich plasma and additionally at 2700 rpm for 10 minutes to obtain platelet-poor plasma. The platelet count was measured with a Sysmex E-2000 (Toa Medical Electronics) and platelet aggregation was induced by ristocetin (Sigma Chemical Co) at a final concentration of 2.0 mg/mL, and the percentage of maximum light transmission was measured with an aggregometer (NBS Hematrac 801, Niko Bioscience, Inc).

**Cell Culture**

SMCs were isolated from the carotid arteries of each guinea pig by an explant method (n=3). Isolated cells (1×10^6 cells per well) from each clone were seeded in 24-well dishes and cultured in DMEM containing 10% FBS at 37°C in a humidified atmosphere of 5% CO2 in air. After 24 hours, antibody was added into the cell culture media. Cells were detached with trypsin and counted with a hemocytometer every day for 3 days.

**Statistics**

All data are expressed as mean ± SEM. ANOVA followed by a Dunnett test or unpaired t test was used for validation of the I/M ratio and platelet aggregation. The Mann-Whitney U test was used for vWF and fibrinogen depositions. In addition, a Fisher exact probability test was performed for the incidence of organized thrombus, and a Spearman rank test was performed for the correlation between the I/M ratio and Th/M ratio. A value of P<0.05 was considered statistically significant.

**Results**

**Ex Vivo Platelet Aggregation**

The ex vivo antiplatelet effect of AJvW-2 in guinea pigs is shown in Figure 1. The ristocetin-induced platelet aggregation was completely inhibited 5 minutes after a bolus injection of AJvW-2 at doses of 0.6 and 1.8 mg/kg. Significant inhibition persisted for at least 1 day at 0.6 mg/kg and for 2 days at 1.8 mg/kg. The effect of a lower dose (0.18 mg/kg) disappeared within 1 day (data not shown).

**Neointima Formation**

Four cases of thrombus-occluded vessels were observed 14 days after angioplasty and were discarded from the present study (2 cases in the control group and 2 cases in the 0.6 mg/kg AJvW-2-treated group). AJvW-2 dose-dependently prevented neointima formation by a bolus injection 14 days after balloon injury (Figure 2). I/M ratios were 0.83±0.11, 0.56±0.14, and 0.29±0.07 in groups treated with saline, 0.6 mg/kg AJvW-2, and 1.8 mg/kg AJvW-2, respectively. A significant inhibition was observed at 1.8 mg/kg (65% reduction), although the lower dose (0.6 mg/kg) showed a trend toward inhibition (33% reduction).

**Correlation Between Organized Thrombus and Neointima Formation**

Figure 3A shows that arteries were completely occluded by thrombus 3 days after injury and that red blood cells penetrated into the medial tear. Figure 3B shows that organized thrombus was measured with a Sysmex E-2000 (Toa Medical Electronics) and platelet-rich plasma. The platelet count was measured at 1100 rpm for 10 minutes to obtain platelet-rich plasma and additionally at 2700 rpm for 10 minutes to obtain platelet-poor plasma. The platelet count was measured with a Sysmex E-2000 (Toa Medical Electronics) and adjusted to 250 000/μL. Platelet aggregation was induced by ristocetin (Sigma Chemical Co) at a final concentration of 2.0 mg/mL, and the percentage of maximum light transmission was measured with an aggregometer (NBS Hematrac 801, Niko Bioscience, Inc).

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thrombi were incorporated into the neointima 14 days after injury. Organized thrombi were observed in 10 of 42 sections in the control group. AJvW-2 markedly reduced the incidence of organized thrombus formation (1 of 40 sections) at 1.8 mg/kg \((P < 0.01)\). A significant positive correlation was observed between the organized thrombus area (Th/M ratio) and the I/M ratio \((r^2 = 0.465, P = 0.025)\).

In addition, we compared the inhibitory effect of 1.8 mg/kg AJvW-2 on neointima formation between the sections with and without organized thrombus. In the sections with organized thrombi, the I/M ratios were 0.54 in one animal treated with AJvW-2 \((n = 1)\) and 1.62 ± 0.33 in the control group \((n = 10)\). Whereas in the sections without organized thrombi, the I/M ratios were 0.25 ± 0.03 in the AJvW-2 group \((n = 39)\) and 0.44 ± 0.04 in the control group \((n = 32, P < 0.01)\). Although AJvW-2 prevented neointima formation in either case, the inhibition was more pronounced in the arteries with thrombus (67% versus 43% in the arteries without thrombus).

**vWF and Fibrin(ogen) Deposition**

For the purpose of evaluating the effect of AJvW-2 on initial thrombus formation after balloon injury, immunohistochemistry was performed with polyclonal antibodies against vWF and fibrin(ogen) as a thrombus marker. Representative photomicrographs are shown in Figure 4 and Figure I (which can be accessed online at www.ahajournals.org). In normal carotid arteries, only endothelial cells were slightly immunoreactive for vWF, and no immunoreactivity for fibrin(ogen) was observed (online Figure IA and IB). One day after injury, despite heparin treatment, both vWF and fibrin(ogen) were deposited in the injured medial tears, where no living cell was observed, coinciding with mural thrombi (Figure 4A and 4B).

The distribution of vWF was consistent with that of fibrin(ogen) in the injured artery. Deposition of both markers on day 1 was markedly decreased in the AJvW-2–treated group compared with the control group (Figure 4C and 4D). On day 3, deposition was still observed and slightly organized (data not shown). On day 7, although less reactivity for both adhesive proteins was observed in the media, the modest neointima was prominently immunoreactive for vWF but not for fibrin(ogen) (data not shown). On day 14, further thickening of intima was observed, and vWF deposits were still present diffusely or prominently in the luminal part of the intima, just beneath the endothelial cells, whereas no immunoreactivity for fibrin(ogen) was observed (online Figure IC and ID).

The summarized results are shown in the Table. Deposition in the media was gradually decreased in the control group for both markers. vWF and fibrin(ogen) deposition in the media was significantly inhibited by a bolus injection of 1.8 mg/kg AJvW-2 (91.5% and 54.5% reduction, respectively) on day 1, although no inhibition was observed on day 3. On the contrary, the deposition of both markers in the intima was not affected by an initial bolus injection of AJvW-2.

**SMC Proliferation**

The direct effect of AJvW-2 on the proliferation of cultured SMCs isolated from guinea pig carotid arteries was investigated. AJvW-2 did not affect the cell growth up to 150 \(\mu\)g/mL, which was 3 times as high as the maximum calculated plasma concentrations achieved by a bolus injection of 1.8 mg/kg AJvW-2 \((2.75 ± 0.58 \times 10^4 \text{ cells per well in the control group on day 3})\). In addition, immunohistochemistry for proliferating cell nuclear antigen showed that AJvW-2 \((1.8 \text{ mg/kg})\) slightly reduced the rate of proliferating SMCs in the media as well as the intima, but not significantly (data not shown).

**Discussion**

The present study was undertaken to investigate whether selective blockade of the GPIb-vWF axis could prevent neointima formation after balloon injury in guinea pigs. The major findings of the present study were that organized...
thrombus contributed to the severity of neointima formation and that the anti-vWF monoclonal antibody AJvW-2 could prevent thrombus deposition and further neointima formation.

Various animal models have been established to investigate the inhibitory effect of pharmacological agents on neointima formation. Although numerous agents, such as heparin, statins, and angiotensin-converting enzyme inhibitors, have shown a significant inhibitory effect on neointima formation in rats, none of them was successful in clinical trials. SMC proliferation was suggested to contribute to neointima formation mainly in rats. However, other components, such as organized thrombi and extracellular matrix changes, were also observed in clinical restenotic lesions, pointing to the study limitation of a rat model of balloon injury. We chose guinea pigs for the present study because they are relatively thrombogenic animals compared with rats. In addition, they are small, easy to handle, and appropriate for the first evaluation of this antibody. Previous studies indicated that thrombosis after balloon injury was a frequent event (33% occlusive thrombi) in guinea pigs, although that was virtually never observed in rats. This difference between species might be attributed to the difference of pros-tacyclin production by the arterial wall. Actually, in our preliminary study, occlusive thrombi and large mural thrombi after balloon injury were observed in 77% and in 19% of injured animals, respectively. Therefore, we used heparin to prevent acute thrombotic occlusion. We also used it because heparin has been routinely used in clinical practice during PTCA procedures.

In this model, some organized thrombi were detected in severely stenosed vessel walls on day 14, which positively correlated with neointimal thickness. In addition, vWF and fibrin(ogen) depositions were observed in the injured medial tears during the early phase. Both adhesive proteins may function as a mediator of platelet-platelet or platelet-vascular interactions and may also be incorporated into α-granules in platelets. These results suggest that immediately after balloon injury, platelet-mediated thrombus was deposited into the injured medial tear. Thereafter, the mural thrombi organized and resulted in the severe luminal narrowing that was due to SMC migration and proliferation in the presence of organized thrombi. Mural thrombi may contribute to neointima formation not only through the growth factors or cytokines released from activated platelets but also by functioning as a scaffold for SMC migration and proliferation.

Our findings were supported by the following previous reports: Recchia et al showed that the degree of luminal stenosis was greater in the presence of lesions containing thrombus than in those without thrombus in hypercholesterolemic pigs. Bosmans et al suggested that fibrin(ogen) and vWF depositions were associated with intimal thickening after balloon angioplasty of the rabbit carotid artery. Furthermore, there was a clinical observation indicating that the presence of angiographically identifiable thrombus at the time of the angioplasty procedure was associated with the higher rate of restenosis.

AJvW-2, a murine monoclonal antibody against human vWF, prevented neointima formation 14 days after balloon injury. Significant decreases in vWF and fibrin(ogen) deposition in the injured media were observed on day 1 in the AJvW-2 group. In addition, AJvW-2 markedly decreased the incidence of organized thrombus formation. AJvW-2 did not affect the proliferation of cultured SMCs or the rate of proliferating cell nuclear antigen–positive SMCs after injury. These results suggest that AJvW-2 prevented neointima formation mainly because of the inhibition of initial platelet-mediated thrombus formation, leading to PDGF release and fibrin formation, which induced SMC migration.

Prominent deposits of vWF, but not fibrin(ogen), in the intima were also observed at 7 and 14 days after injury in the present study. Previous reports have suggested that vWF deposition is associated with neointima formation after balloon injury or collar placement in normocholesterolemic rabbits as well as with atherosclerotic plaque formation in

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**Deposition of vWF and Fibrin(ogen) in Injured Media and Neointima After Administration of AJvW-2 (1.8 mg/kg)**

<table>
<thead>
<tr>
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<th>Day 1</th>
<th>Day 3</th>
<th>Day 7</th>
<th>Day 14</th>
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<td><strong>vWF-positive area, %</strong></td>
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<tr>
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<td>1.0±0.3</td>
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<tr>
<td>Control</td>
<td>19.4±3.5</td>
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<td>1.7±0.8</td>
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<td>2.0±0.5</td>
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</table>

Data are mean±SEM.

*P<0.05 vs each control by Mann-Whitney U test.
cholesterol-fed rabbits. Although the role of vWF deposition in the intima remains unclear, the presence of vWF was not affected by the initial injection of AjvW-2.

Previous studies have demonstrated that the GPIb-vWF axis might be involved in neointima formation in experimental animal models. The recombinant vWF A1 domain fragment (VCL) prevented neointima formation in rats by an intravenous infusion for 72 hours. In addition, a fractionated aurintricarboxylic acid prevented neointima formation in hamsters by an intravenous infusion for 7 days. However, aurintricarboxylic acid is a multimeric molecular mixture that binds to vWF and has also been reported to prolong the coagulation parameters, thus complicating the understanding of its effect on neointima formation. In addition, VCL is an antagonist of GPIb but not of vWF, and it is an unstable molecule. In the present study, we showed that the specific and stable blockade of the GPIb-vWF axis with AjvW-2 led to the prevention of neointima formation with no changes in platelet count, prothrombin time, activated partial thromboplastin time, and plasma vWF antigen level (data not shown).

The significant inhibition of neointima formation was observed with a single bolus injection of AjvW-2, which would be a great advantage in clinical application. In the present study, the significant inhibition of platelet aggregation persisted for 2 days by injection of the effective dose (1.8 mg/kg). These results suggest that the blockade of the GPIb-vWF axis might be required for at least 2 days after balloon injury to show a significant inhibition of neointima formation in guinea pigs. No inhibitory effects on the deposition of vWF and fibrin(ogen) were observed on day 3, when the antiplatelet effect of AjvW-2 disappeared, and a slight increase was observed in only the AjvW-2 group. These results suggest that a more potent inhibitory effect on neointima formation would be expected if a longer duration of the antithrombotic effect of AjvW-2 is achieved.

However, the effective dose (1.8 mg/kg) in the present study is already very high, because AjvW-2 has previously been shown to produce a marked inhibition against acute thrombosis at 0.3 mg/kg in guinea pigs. Because AjvW-2 might be rapidly cleared (eg, as a result of its immunogenicity for guinea pigs), an excessive bolus dose might be required to maintain an effective plasma concentration for 2 days. In another study, the repetitive administration of 0.6 mg/kg for an initial 4 days (from 1 day before to 2 days after injury) also significantly prevented neointima formation (data not shown).

In conclusion, the anti-vWF monoclonal antibody AjvW-2 prevented neointima formation by a single bolus injection in guinea pigs. This inhibitory action might be due to the inhibition of initial thrombus deposition (thus avoiding thrombus organization and severe luminal narrowing) rather than the direct inhibition of SMC proliferation. These results suggest that AjvW-2 may be a therapeutic agent for the prevention of acute thrombosis as well as restenosis in clinical practice.

References


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