

Batimastat-Eluting Stent Implantation for the Treatment of Coronary Artery Disease. Results of the Brazilian Pilot Study

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Objective

The excellent results obtained with sirolimus (rapamicin)-eluting stents for preventing restenosis have motivated the evaluation of other substances with that property. Batimastat is a highly effective metalloproteinase enzyme blocker, with the potential to reduce the degradation of extracellular matrix and to inhibit the migration of smooth muscle cells, with the consequent capacity to control coronary restenosis.

Methods

From October 2001 to April 2002, 34 patients were prospectively selected with *de novo* lesions in a native coronary artery $\geq 50\%$ and $< 100\%$, which could be treated with stents of 3 to 4 mm in diameter and 18 mm in length. The primary outcome of the study was to assess the occurrence of major cardiovascular events (death of cardiac origin, acute myocardial infarction, and the need for revascularizing the target vessel) by the 30th day and fourth month; the secondary outcome of the study was to assess the rate of coronary restenosis 4 months after implantation and subacute thrombosis by the 30th day.

Results

The success rate of the procedure was 97.1%. The primary outcome occurred in 2.9% and 27.2% of the patients by the 30th day and fourth month, respectively. The binary restenosis rate on angiography was 39.3%. No episode of subacute thrombosis occurred. The comparative analysis between groups with and without restenosis showed no significant difference between both, except for late luminal loss, which was greater in G-I.

Conclusion

Batimastat-eluting stents had a good safety profile; however, they were not effective in controlling coronary restenosis.

Key words

restenosis, coronary stent, coronary angioplasty

Coronary stents have proved to be better than balloon catheters, because they provide greater safety to the procedure, greater immediate luminal gain, and a smaller rate of restenosis^{1,2}. Despite these benefits, the incidence of coronary restenosis remains elevated, being $> 30\%$ in certain groups of patients³⁻⁶.

The mechanisms involved in the appearance of restenosis are as follows: negative remodeling of the vessel, local formation of thrombus, neointimal proliferation, and excessive production of extracellular matrix⁷⁻⁹.

An alteration in collagen metabolism has been shown to be probably involved in the restenosis process¹⁰. The metalloproteinase enzyme (MP), which has the capacity to degrade collagen and other proteins, such as elastin and proteoglycans¹¹, facilitating the migration of smooth muscle cells, has an increased activity after injury with a balloon catheter¹²⁻¹⁴. Thus, batimastat (BB94), a nonspecific inhibitor of that enzyme, is potentially useful in controlling coronary restenosis.

This study assessed the clinical and angiographic results of batimastat-eluting coronary stents in the treatment of coronary artery disease.

Methods

The stents used in this study were composed of stainless steel and coated with a phosphorylcholine polymer (PC) of the BiodivYsio Drug Delivery (DD) PC-Stent system of Biocompatibles, immersed in a solution containing batimastat at the dosage of 2.0 μg per mm of stent. The PC's coating has the capacity to absorb approximately 30 μg of the drug, a dose that proved effective in studies with animal models. In vitro studies have estimated the period of batimastat release at 24 days (T100%), while in vivo studies have estimated it at 28 days (T99%). The use of batimastat-eluting stents showed no evidence of systemic events in a 6-month follow-up in rats and rabbits receiving the drug intraperitoneally and undergoing balloon angioplasty.

The study protocol was approved by the committee on ethics in research, and all patients signed a written informed consent.

This study prospectively selected patients older than 18 years diagnosed with stable or unstable angina or documented silent ischemia, who had *de novo* lesions < 18 mm in length in a native coronary artery, and stenosis $\geq 50\%$ and $< 100\%$ in vessels whose diameters ranged from 3 to 4 mm. The left ventricular ejection fraction should be $> 30\%$.

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The exclusion criteria were as follows: life expectancy < 9 months; need for great surgical intervention during the 6 months studied; acute myocardial infarction within the preceding 30 days; serum creatinine values > 2.0 mg/dL; platelet count < 100,000 cells/mm³; insulin-dependent or noninsulin-dependent diabetic patients; restenotic lesions; lesions in saphenous or aorto-ostial bypass grafts; contraindications for the use of recommended medications; and, finally, patients who had participated in another investigational study with drugs or devices in the preceding 30 days.

The patients were medicated with 200 mg of acetylsalicylic acid and 75 mg of clopidogrel or 250 mg ticlopidine twice a day, initiated 3 days before the procedure. Aspirin was indefinitely maintained, and clopidogrel or ticlopidine was maintained for 3 months.

Initial laboratory assessment included the following measurements: hemoglobin, hematocrit, leukocytes, sodium, potassium, urea, creatinine, GOT, GPT, CK-MB. The 12-lead ECG was performed 24 hours before and every 8 hours after the procedure.

In the hemodynamic laboratory, after placement of the arterial introducer, heparin was administered aiming at maintaining ACT between 250 and 300 seconds. Nitroglycerin was injected intracoronarily at the dosage of 50 to 200 µg, and 2 orthogonal projections where the lesion to be treated was better visualized were filmed.

Stents were implanted after lesion predilation with a balloon catheter. Eleven-, 15-, and 18-mm-long and 3.0-, 3.5-, and 4.0-mm-diameter stents were used. We tried to maintain a balloon/artery ratio of 1:1.

The hemodynamic parameters analyzed by the investigators with digital quantitative angiography performed in a Phillips H 5000 device before and after stent implantation were as follows: minimum luminal diameter, reference diameter, percentage of stenosis, and late luminal loss. Success of the procedure was defined as a residual lesion < 10% and normal coronary flow obtainment (TIMI III).

After the procedure, the introducer was withdrawn when ACT was < 180 seconds. CK-MB measurements were taken every 8 hours. GP IIb/IIIa inhibitor was not used.

Assessment of patients after 1 and 4 months included: anamnesis, physical examination, ECG, hemogram, and serum measurements of Na⁺, K⁺, urea, creatinine, GOT, and GPT.

Control coronary angiography was performed, on average, 4±1 months after stent implantation. Restenosis was considered a vessel lumen obstruction ≥ 50%.

The primary outcome of the study was to assess the occurrence of major cardiac events (death of cardiac origin, acute myocardial infarction, and the need for revascularization of the target vessel) by the 30th day and the fourth month. Acute myocardial infarction was defined as "Q" when CKMB levels increased more than 2.5 times its normal value, and new Q waves appeared in at least 2 contiguous leads on an electrocardiogram. The acute myocardial infarction was defined as "non Q" when only the enzymatic elevation was observed.

The secondary outcomes included binary restenosis by the fourth month (stenosis ≥ 50% of the luminal diameter) and incidence of subacute thrombosis of the stent by the 30th day.

The continuous variables were expressed as mean and standard deviation and analyzed by using the Student *t* test. The categorical variables were expressed as percentages and compared by using the Fisher exact test. The significance level of P<0.05 was adopted.

Results

From October 2001 to April 2002, 34 patients underwent batimastat-eluting stent implantation. Their basic clinical characteristics are shown in table I.

The procedure was successful in 33 (97.1%) patients. In one patient, progression of the stent was not possible due to marked tortuosity of the coronary artery. As the stent could not be implanted in the lesion, the patient was excluded from the study.

One (2.9%) patient had non-Q acute myocardial infarction in the in-hospital phase. Primary outcome of eligible patients on the fourth month was 27.2%, due exclusively to the need for revascularization of the target vessel. The major adverse cardiac events are shown in table II.

Subacute thrombosis of the stent was observed neither by the 30th day, nor after 4 months. Binary restenosis by the fourth month was observed in 13 of the 33 (39.3%) eligible patients.

Because of the high restenosis rate found, and in an attempt to identify a possible determining factor, the patients were divided into 2 groups as follows: G-I, patients with restenosis; and G-II, patients with no restenosis. However, the comparative analysis showed no differences between both groups regarding the major clinical and angiographic variables associated with the restenosis process (tab. III).

Table I - Basic characteristics of the entire population

	n=34
Age (years)	56±10.5
Female sex	6 (17.6%)
Previous AMI	8 (23.5%)
Dyslipidemia	8 (23.5%)
Hypertension	23 (67.6%)
Smoking	13 (38.2%)
Stable angina	22 (64.7%)
Unstable angina	5 (14.7%)
Silent ischemia	7 (20.6%)
Vessel treated	
Anterior Descending	16 (47.1%)
Right Coronary	13 (38.2%)
Circunflex	5 (14.7%)
Type of lesion	
A + B1	10 (29.4%)
B2	17 (50.0%)
C	8 (23.5%)
Length of lesion > 20 mm	0
Stent length 11 mm	12 (35.3%)
Stent length 15 mm	14 (41.2%)
Stent length 18 mm	8 (23.5%)
Stent diameter 3.0 mm	15 (44.1%)
Stent diameter 3.5 mm	18 (52.9%)
Stent diameter 4.0 mm	1 (2.9%)
Deployment pressure	14.7±1.7

Table II - Primary outcome (major cardiac events)

	30 days	4 months
Death of cardiac origin	0	0
AMI*	1 (2.9%)	0
RTV†	0	9 (27.2%)
New CTA‡	0	7 (21.2%)
Surgery	0	2 (6.0%)

*Acute myocardial infarction; †Revascularization of the target vessel; ‡Coronary transluminal angioplasty.



Table III – Basic characteristics of the groups with (G-I) and without (G-II) restenosis*		
	G-I n=13	G-II n=20
Age (years)	56±9.6	56±11.6
Female sex	3 (23%)	3 (15%)
Previous AMI	2 (15%)	5 (25%)
Dyslipidemia	1 (7%)	6 (30%)
Hypertension	8 (61%)	14 (70%)
Smoking	6 (46%)	7 (35%)
Stable angina	9 (69%)	13 (65%)
Unstable angina	1 (7%)	3 (15%)
Silent ischemia	3 (23%)	4 (20%)
Vessel treated		
Anterior Descending	8 (61%)	8 (40%)
Right Coronary	3 (23%)	9 (45%)
Circunflex	2 (15%)	3 (15%)
Type of lesion		
A + B1	2 (15%)	8 (40%)
B2	8 (61%)	10 (50%)
C	3 (23%)	2 (10%)
Length of lesion > 20 mm	0	0
Stent length 11 mm	5 (38%)	6 (30%)
Stent length 15 mm	3 (23%)	11 (55%)
Stent length 18 mm	5 (38%)	3 (15%)
Stent diameter 3.0 mm	9 (69%)	6 (30%)
Stent diameter 3.5 mm	4 (30%)	13 (65%)
Stent diameter 4.0 mm	0	1 (5%)
Deployment pressure (atm)	14±1.8	15±1.5

* No significant difference was observed between G-I and G-II (P = ns).

Table IV - Results of the digital quantitative angiography			
	Total n=33	G-I n=13	G-II n=20
RD (mm)*			
Pre	2.98 ±0.39	2.86 ±0.34	3.10 ±0.46
Post	3.04 ±0.36	2.94 ±0.37	3.15 ±0.36
4 months	3.01 ±0.58	3.09 ±0.54	2.94 ±0.64
MLD (mm) †			
Pre	0.83 ±0.41	0.69 ±0.43	0.98 ±0.38
Post	3.06 ±0.40	2.97 ±0.44	3.15 ±0.38
4 months	1.77 ±0.83	1.27 ±0.90	2.28 ±0.75
% stenosis			
Pre	87.50 ± 9.10	89.66 ± 8.92	85.35 ± 9.27
Post	2.32 ± 3.42	1.43 ± 2.99	3.22 ± 4.68
4 months	44.36 ±12.82	66.08 ±10.84	22.65 ±15.42
LLL (mm)‡	1.29 ± 0.53	1.70 ± 0.51	0.87 ± 0.51 &

* Reference diameter of the vessel; † Minimum luminal diameter; ‡Late luminal loss; & = P < 0.05.

The results of digital quantitative angiography, including late luminal loss (LLL), defined as the difference between the minimum luminal diameter (MLD) immediately after stent implantation and MLD in the fourth month, are listed in table IV. Significant differences were observed only in the LLL, which were greater in G-I.

Discussion

Despite the use of stents, coronary restenosis has been the limiting factor of the percutaneous coronary revascularization success in the long run^{1,2}.

Some techniques, such as brachytherapy¹⁵, rotational and directional atherectomy, and excimer laser¹⁶⁻¹⁸, have been used to control restenosis, but with limited results.

Restenosis after stent implantation occurs as a result of the proliferation and migration of smooth muscle cells (SMC) to the vascular lumen and the excessive production of extracellular matrix¹⁹⁻²². The metalloproteinase (MP) enzymes involved in migration of the SMC and that belong to the group of proteinases may be subdivided into 3 classes: collagenases, stromelysines, and gelatinases. Those enzymes can degrade the components of the extracellular matrix, including collagen, and the glycoprotein membrane, therefore, facilitating the migration of smooth muscle cells²³.

Batimastat is a low-molecular-weight mimetic peptide containing a hydroxamate group responsible by chelation of the zinc atom in the active site of the metalloproteinases, therefore inhibiting the action of that enzyme. It was initially used as an oncologic drug²⁴.

Studies with animals have shown that batimastat was effective

in preventing both negative arterial remodeling and late luminal loss after balloon catheter angioplasty²⁵⁻²⁷.

In this study, the use of batimastat-eluting stents proved to be safe; neither thrombosis of the stent, nor any detectable deleterious effect of the drug was observed. However, control neither of angiographic restenosis (38.2%), nor of the need for new revascularization (27.2%), was observed in the fourth month. Analysis of the subgroups of patients with and without restenosis showed no significant differences when comparing the clinical and angiographic variables.

Our results are in accordance with those of the unpublished European prospective nonrandomized multicentric study, Brilliant I (batimastat anti-restenosis trial utilizing the BiodivYsio local drug delivery PC stent), which selected 173 patients with de novo lesions in native coronary arteries. Thirty days after implantation, 2 (1.2%) patients had non-Q acute myocardial infarction related to the procedure, and the 6-month angiographic control showed a binary restenosis rate of 25%.

Recent randomized studies²⁸⁻³² using sirolimus (rapamicin)- and paclitaxel-eluting stents, whose action mechanism differs from that of batimastat, had extremely favorable results, with a significant decrease in the restenosis rate and in the need for revascularization of the target lesion. The angiographic analysis and intracoronary ultrasound in one of those studies showed sustained suppression of neointimal proliferation one year after implantation³³. Those findings have shown that drug-eluting stents are a safe and effective form of treatment, with the potential to change coronary artery disease therapy in the future.

Other drugs, such as stradiol^{34,35}, tacrolimus³⁶, and everolimus³⁷, have been investigated with good initial results, and they may soon be available for daily use, enlarging the treatment options and contributing to reduce the cost of the procedure.

In conclusion, our results showed that batimastat-eluting stents, at the recommended dosage and with the release kinetic used, were not effective in inhibiting coronary restenosis; it even showed greater rates than those reported in the SOPHOS study³⁸, in which the BiodivYsio stent was used without drug elution.

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