Janus® Tacrolimus-Eluting Carbostent. Immediate and Medium-Term Clinical Results

Julio García-Tejada, Hipólito Gutiérrez, Agustín Albarrán, Felipe Hernández, Teresa Velázquez, Sergio Rodríguez, Iván Gómez, and Juan Tascón

Servicio de Cardiología, Hospital 12 de Octubre, Madrid, Spain

This observational and clinical follow-up study involved the first 50 patients who were treated with the Janus® tacrolimus-eluting carbostent (Sorin Group) at our hospital. The patients' mean age was 66 (10) years, 38% were diabetic, and 56% were admitted with acute coronary syndrome. In total, 56 lesions were treated (52% were type B2/C), of which 12% involved in-stent restenosis, 5% were chronic occlusions, 23% were long lesions (>20 mm), 25% were in small vessels (≤2.5 mm), 7% were aorto-ostial lesions, 5% were in vein grafts, and 14% involved angiographically visible thrombus. Some 63 Janus® carbostents were implanted (ie, 1.26 [0.49] stents/patient). A successful outcome was achieved for all lesions. One patient (2%) required reintervention at the target lesion because of acute thrombosis. During a follow-up period of 10 (3) months, 8 (16%) major adverse cardiac events occurred: there was 1 (2%) death due to heart failure and 7 patients (14%) required revascularization, in 5 (10%) cases because of restenosis of the Janus® carbostent.

Key words: *Stent. Coronary angioplasty. Prognosis.*

Carbo-*stent* liberador de tacrolimus Janus®. Resultados inmediatos y seguimiento clínico a medio plazo

Estudio observacional con seguimiento clínico de los primeros 50 pacientes tratados en nuestro centro con el carbo-*stent* de tacrolimus Janus® (Sorin Group). La edad media de los pacientes fue 66 ± 10 años. El 38% era diabético y el 56% ingresó por un síndrome coronario agudo. Se trataron 56 lesiones (el 52% de tipo B2/C), incluidos un 12% de reestenosis intra-*stent,* un 5% de oclusiones crónicas, un 23% de lesiones difusas (> 20 mm), un 25% de lesiones en vaso pequeño (≤ 2,5 mm), un 7% de lesiones aortoostiales, un 5% de lesiones en puentes de safena y un 14% con trombo angiográfico. Se implantaron 63 carbo-*stents* Janus® (1,26 ± 0,49 *stents*/paciente). Se obtuvo éxito inmediato en todas las lesiones. Un paciente precisó reintervención de la lesión tratada por trombosis aguda (2%). Tras un seguimiento de 10 ± 3 meses se han producido 8 eventos adversos cardiacos mayores (16%): una muerte por insuficiencia cardiaca (2%) y 7 nuevos procedimientos de revascularización (14%), de los que 5 se debieron a reestenosis de carbo-*stents* Janus® (10%).

Palabras clave: Stent. *Angioplastia coronaria. Pronóstico.*

INTRODUCTION

The Janus® Tacrolimus-eluting carbostent (JTS) has obtained favorable results in experimental animal studies with regard to the bioavailability of the drug and its antiproliferative effect. The surface of the JTS is coated with Carbofilm™ a substance with proven biocompatibility and thromboresistance.[1] The design of this stent incorporates microreservoirs that achieve local deposit of the drug, which is released directly to the vessel wall.

Recently the results of the JUPITER I and II studies have been described, in which the JTS was found to be a safe device for treating uncomplicated coronary lesions.[2,3] Among the selection criteria for these studies, unfavorable clinical scenarios and complex lesions were excluded. The aim of the present study was to assess the safety and clinical efficacy of the JTS for the treatment of an unselected population of patients with coronary disease, without application of restrictive clinical or anatomical criteria.

METHODS

Population

The series includes the first 50 patients (56 lesions) treated with the JTS in our center. The procedures were carried out between February and August 2005, and the patients were followed-up until May 2006. The characteristics of the patients and the lesions are shown in Tables 1 and 2. It is worth noting that 84% of the patients presented at least one clinical or angiographic

Correspondence: Dr. J. García Tejada.
Servicio de Cardiología. Hospital 12 de Octubre.
Avda. Córdoba, s/n. 28045 Madrid. España.
E-mail: juliogtejada@yahoo.com

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TABLE 1. **Characteristics of the Patients and Lesions***

Age (range)	66.1 (10.1) (43-82)
Diabetes mellitus	19 (38%)
Prior AMI	16 (32%)
Prior PCI	18 (36%)
Prior surgery	8 (16%)
GPI IIb/IIIa	11 (22%)
Acute coronary syndrome	28 (56%)
Primary PCI	3 (6%)
Multivessel disease	34 (68%)
ACC/AHA type B2/C	19 (52%)
Moderate-severe calcification	16 (28.6%)
Thrombus	8 (14.3%)
Bifurcation	11 (19.6%)
Restenosis	7 (12.5%)
Diffuse (>20 mm)	13 (23.2%)
Small vessel (≤2.5 mm)	14 (25%)
Subacute or chronic occlusion	6 (11)
Pre-PCI TIMI <III	19 (34%)
Reference diameter, mm	2.76 (0.31)
Pre-PCI MLD, mm	0.71 (0.40)
Length, mm	18.12 (0.35)

*AMI indicates acute myocardial infarction; GPI, glycoprotein inhibitors; HT, hypertension; MLD, minimum lumen diameter; PCI, percutaneous coronary intervention.

TABLE 2. **Clinical Events During Outpatient Follow-Up (n=50)***

MACE	8 (16%)
Death	1 (2%)
AMI	0 (0%)
New revascularization procedure:	7 (14%)
For a lesion treated with a Janus® carbostent	5 (10%)
For another lesion	2 (4%)
Subacute or late thrombosis	0 (0%)
Stroke	2 (4%)

*AMI, indicates acute myocardial infarction; MACE, major adverse cardiac events.

characteristic considered to be an exclusion criterion in the JUPITER-II[3] study.

Angioplasty Procedure

The procedures were performed through a femoral access in 48 patients and a radial access in 2 patients. Selection of the guide catheter and the use of glycoprotein inhibitors (GPI) IIb/IIIa was left to the discretion of the operator. All patients received a heparin bolus of 1 mg/kg of body weight (or 0.5 mg/kg when concomitant GPI IIb/IIIa was used) at the start of the procedure. Direct implantation of the JTS was performed in 53.6% of the lesions. An oral dose of 300 mg of clopidogrel was administered immediately after the procedure in patients who had not received it previously. Thereafter, patients continued with daily treatment of 100 mg of acetylsalicylic acid indefinitely and 75 mg of clopidogrel for 6 months.

Follow-Up

Electrocardiography and creatine kinase (CK) determinations were carried out immediately and at 8, 16, and 24 h following the procedure. After hospital discharge, follow-up was performed by telephone contact or by medical visits at 1 month and 6 months, and a test for detection of ischemia was scheduled at 6 months following the procedure. Coronary angiography was performed when there were recurrent symptoms or when ischemia was documented on the noninvasive tests, at the discretion of the cardiologist attending the patient. The development of major adverse cardiac events (MACE) was recorded: death, infarction, stent thrombosis, and the need for a new revascularization procedure.

RESULTS

Procedural and Hospital Outcomes

Immediate angiographic success was obtained in all the lesions treated. There was one case of acute thrombosis that led to a non-Q wave infarction (maximum CK, 630 U). The patient was diabetic and had a long lesion in the middle left anterior descending artery, which had been treated with 2 JTS. The patient had not been pretreated with clopidogrel and GPI IIb/IIIa had not been used. At 2 h following the initial procedure, the patient presented angina and ST segment elevation in V_1 through V_4. Emergency coronary angiography showed an in-stent thrombotic occlusion. Abciximab was administered and the thrombotic material was successfully extracted with use of an Export® device (Medtronic). In addition, an evaluation with intravascular ultrasonography was performed, which showed insufficient expansion and inadequate apposition of the two stents, as well as a small space between the stents that was not covered. Implantation of a new JTS was decided with subsequent balloon dilation, which had a good angiographic and sonographic outcome. There were no other MACE during hospitalization. One patient presented a retroperitoneal hematoma that required treatment with plasma expanders and packed red blood cell transfusion, with a good evolution thereafter.

Outpatient Follow-Up

Clinical follow-up lasted 10 (3) months, with at least 6 months of follow-up in all patients. In addition, an ischemia test was carried out in 86% of patients. During the outpatient follow-up, 8 (16%) patients presented some type of MACE. There was one death due to heart failure at the fifth month following the procedure in a patient who had dilated cardiomyopathy with severe ventricular

dysfunction. Seven patients (14%) required a new revascularization procedure: in 5 (10%) of them, coronary angiography showed significant restenosis of a JTS; the other 2 patients (4%) had restenosis of other previously implanted stents, whereas the JTS did not present restenosis. The 5 patients with JTS restenosis were diabetic. New revascularization procedures were needed in 26.3% of patients with diabetes and in 6.4% of non-diabetic patients. Among the 5 patients with JTS restenosis, the restenosis pattern was focal in 2 (in-stent in one and at the proximal end in the other) and diffuse in 3 patients.

Another 6 patients presented chest pain during follow-up. In 3 of them, a new coronary angiography study showed no JTS stenosis. The other 3 patients, who had inducible angina and ischemia before the initial procedure and had been asymptomatic following the intervention, presented atypical chest pain. The patients underwent stress testing, which showed no ischemia; hence, an angiographic study was not performed.

Lastly, another 5 patients presented inducible ischemia in the prognostic tests performed during follow-up: in 3 of them angiography showed no restenosis of the JTS. In the other 2 patients anti-anginal treatment was increased, since the patients had multivessel disease and incomplete revascularization, with inducible ischemia at high doses. Moreover, the isotopes only showed ischemia in a territory that was not dependent on the stented artery; therefore, angiography was not performed.

There were no cases of subacute or delayed thrombosis over the follow-up period. The patient with acute thrombosis had negative stress test results at 6 months of follow-up and is asymptomatic at the time of writing.

DISCUSSION

Comparison With Previous Studies

In the JUPITER-II study, 163 patients treated with JTS were compared with 163 patients treated with the same stent without the drug. There were no significant differences between the groups with regard to late lumen loss (primary endpoint of the study) or rate of revascularization of the treated lesion target lesion revascularization (TLR).[3] In the group of patients receiving a JTS, the TLR rate was 5.7% and the in-stent late lumen loss was 0.63 mm in both groups. These values are higher than the reported rates in the initial randomized studies with the Cypher® or Taxus® stents, carried out in patients and lesions having similar characteristics.[4,5]

In our initial series of 50 patients treated with JTS stents, following a mean follow-up period of 10 months, the rate of new revascularization procedures was 14% (7 patients), among which 10% (5 patients) were required in patients with JTS restenosis. This value is higher than the rate reported in the JUPITER-II study, but the difference can be explained by the greater clinical and anatomical complexity of our patients. It is also higher than the rates found in registries performed with the Cypher® or Taxus® stents in populations with clinical and angiographic characteristics similar to those of the patients in our series.[6,7] Whether these differences are due to the characteristics of the stent platform or the potency, dose, or kinetics of tacrolimus release, will require clarification in future studies with a larger number of patients.

Di Salvo et al[8] recently described the results of a series of 112 unselected patients (142 lesions) treated with the JTS. The authors reported 2 cases (1.8%) of acute thrombosis and a MACE rate of 0%, but the clinical follow-up lasted only 3 months. To our knowledge, apart from the JUPITER studies, no other reports on the JTS in the scientific literature have a longer follow-up.

In the main studies[4-6] performed with the Cypher® and Taxus® stents, as well as in the JUPITER-I[2] study, diabetic patients presented higher rates of restenosis and TLR than nondiabetic patients. In addition to diabetes, certain anatomic variables (long, restenotic, ostial, or small vessel lesions) were associated with a greater risk of restenosis following implantation of a drug-eluting stent, particularly when several of these factors are present simultaneously.[9-11] The 5 patients in our study who required TLR due to JTS restenosis were diabetic. Moreover, 3 of them had long lesions and small-vessel lesions, and one was a restenotic lesion in a previously implanted drug-eluting stent.

Stent Thrombosis and Antiplatelet Treatment

In the JUPITER-II study there were no cases of thrombosis in patients treated with a JTS, despite the fact that 40% took double antiplatelet therapy for only 3 months.[3] In the series of di Salvo et al,[8] however, there were 2 cases of acute thrombosis (1.8%), an incidence similar to that of our patients. The only case of thrombosis in our study occurred acutely and we believe that this complication was not related to the design or characteristics of the JTS, but rather to inadequate technique. In this regard, careful inspection to detect residual dissection and the use of intravascular ultrasound to assure proper stent apposition and complete coverage of the lesion can avoid this complication.[9] No other cases of acute or subacute thrombosis were produced in our series, despite the high frequency of diabetic and unstable patients and patients with angiographic thrombus, and despite the relatively low utilization of GPI IIb/IIIa.

Because of the lack of consensus in the scientific literature,[9] we maintained double antiplatelet therapy for 6 months in this study, as is the routine practice in our laboratory with other drug eluting stents. There were no cases of late thrombosis with this regimen, a fact that further supports the safety of the JTS manifested in the JUPITER studies.

Limitations

The relatively small number of patients and the absence of a control group are the main limitations of this study. We did not perform an angiographic control in the follow-up of the patients. Nonetheless, we consider that clinical restenosis is the true determinant of the impact this problem has on health care. Therefore, clinical follow-up and the ischemia test at 6 months, which is routinely done in our center, adheres more closely to the reality of daily practice than systematic coronary angiography in all patients.

REFERENCES

1. Bartorelli AL, Trabattoni D, Montorsi P, Fabbiocchi F, Galli S, Ravagnami P, et al. Aspirin alone antiplatelet regimen after intracoronary placement of Carbostent™: The ANTARES study. Catheter cardiovasc Interv. 2002;55:150-6.
2. Bartorelli AL. Tacrolimus drug-eluting stents. The Sorin JANUS FIM results (JUPITER I) and new clinical trial insights. Sesiones científicas del TCT, 2004 [consultado 1 Mar 2006]. Disponible en: http://www.tctmd.com/csportal/ShowBinary/BEA%20Repository/TCTMD%20Portal/EPSlidePressPool/ExpertPresentation_1114118613886//pdfFile
3. Morice MC. JUPITER II: doble blind randomized comparison of Janus tacrolimus eluting stent with the Tecnic carbostent. Sesiones científicas del TCT, 2005 [accedido 1 Mar 2006]. Disponible en: http://www.tctmd.com/csportal/ShowBinary/BEA%20Repository/TCTMD%20Portal/EPSlidePressPoolNew/2005/Oct2005Slides/Morice_T05_T1100//pdfFile
4. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med. 2002;346:1773-80.
5. Stone GW, Ellis SG, Cox DA, Hermiller J, Oshaughnessy C, Mann JT, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med. 2004;350:221-31.
6. Ong ATL, Serruys PW, Aoki J, Hoye A, Van Mieghem CA, Rodríguez-Granillo GA, et al. The unrestricted use of paclitaxel- versus sirolimus-eluting stents for coronary artery disease in an unselected population. One-year results of the Taxus-Stent Evaluated At Rotterdam Cardiology Hospital (T-RESEARCH) Registry. J Am Coll Cardiol. 2005;45:1135-41.
7. De la Torre JM, Sainz Laso F, Ruisánchez C, Zueco J, Figueroa A, Colman T. [Treatment of lesions with a high risk of stenosis. Comparative study in 300 patients of rapamycin- and paclitaxel-eluting polymer-based stent, and bare metal stents.] Rev Esp Cardiol. 2005;58:262-9.
8. Di Salvo MA, Aiello R, Scardaci F, Parisi R, Garro N, Galassi AR, et al. Tacrolimus eluting stenting in coronary artery lesions: immediate results, one and three month outcome [abstract]. Am J Cardiol. 2005;96:208H.
9. Salam AM, Suwuaidi A, Holmes Jr DR. Drug-eluting coronary stents. Curr Probl Cardiol. 2006;31:8-119.
10. De la Torre Hernández JM, Burgos V, González-Enríquez S, Cobo M, Zueco J, Figueroa A, et al. *Stent* liberador de rapamicina en el tratamiento de lesiones coronarias de alto riesgo de reestenosis. Seguimiento clínico a 6 meses de los primeros 100 pacientes. Rev Esp Cardiol. 2004;57:116-22.
11. Ruiz-Nodar JM, Frutos A, Carrillo P, Morillas P, Valero R, Rodríguez JA, et al. Utilización del *stent* recubierto de rapamicina en la revascularización de lesiones complejas: estudio con seguimiento clínico y angiográfico. Rev Esp Cardiol. 2004;57:123-9.