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A Prospective Single-Centre Non- Randomized Study to Investigate Safety and Efficacy of M'Sure-S with ultra-low thickness (59µm), (Sirolimus Eluting Coronary Stent)

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Short title: PRISM-PILOT- A Prospective Single-Centre Non- Randomized Study to Investigate Safety and Efficacy of M'Sure-S (Sirolimus Eluting Coronary Stent), with ultra low strut thickness of 59 µm

Abstract

Background: The development of DES has been pioneered through a combination of the increased understanding of the biology of restenosis, the selection of drugs that target 1 or more pathways in the restenotic process, controlled-release drug delivery strategies, and the use of the stent as a delivery platform. M'Sure-S, Sirolimus-eluting stent (SES) is an indigenously developed generic drug eluting coronary stent system. The stent has a strut of ultra-low thickness (59µm), a cobalt–chromium (L605) platform using an intelligent cell design allowing high radial strength and good flexibility. The drug used is Sirolimus, which is a cytostatic, non proliferative drug which elutes from biodegradable copolymer formulation within 28 to 30 days time.

Methods: The PRISM Pilot is a prospective, single-centre, non- randomized Study to Investigate the safety and efficacy of M'Sure-S in 32 patients with a single de novo lesion in native coronary arteries. The primary safety and efficacy end-points were major adverse cardiac events (MACE) at 30 days and in-stent late lumen loss at six months, measured using QCA. Secondary safety and efficacy end-points included angiographic binary restenosis at Six month angiographic follow-up. Other end-points included the occurrence of stent thrombosis (acute, subacute, late and very late), percentage of diameter stenosis measured by QCA.

Results: No MACE was observed and the median in-stent late luminal loss in 27 subjects studied by QCA was 0.05 mm, with 0% binary restenosis at six month angiographic follow-up. No stent thrombosis was observed up to six month follow up.

Conclusions: M'Sure-S, in comparison to currently marketed DES, appears to have a considerable scientific basis for prevention of neointimal proliferation, restenosis and associated clinical events.

Introduction

The PRISM Pilot study is being conducted to determine the safety and efficacy of the new-generation Sirolimus-eluting stent (SES), M'Sure-S. It uses non-inflammatory, biodegradable, biocompatible polymers eluted from a very low strut thickness. M'Sure-S is an intelligently designed Stent which helps early endothelialization, thus reducing/eliminating early or late complications, such MACE and stent thrombosis.

Methods

The PRISM Pilot study has a prospective, single-centre, nonrandomized, open-label study. Patients were considered to be eligible if they were above 18 years of age, acceptable candidate for PTCA, Stenting, or Emergent CABG and presented with Symptomatic ischemic heart disease and/or objective evidence of myocardial ischemia. The essential inclusion criteria was the presence of a de novo target lesion located in the native coronary artery that was suitable to conventional angioplasty and stenting techniques which can be covered by one stent, no overlapping allowed.

The main exclusion criteria were; Pregnancy, known hypersensitivity/contraindication to Sirolimus or any other mTOR inhibitor, hypersensitivity/contraindication to aspirin, clopidogrel or other thienopyridines and hypersensitivity/contraindication to cobalt, chromium, heparin or contrast media that are routinely present during stent procedures.

Other exclusion criteria included; pretreatment of target lesions by stenting methods, previous brachytherapy, presence of significant non-target lesions requiring treatment within 30 days of the index procedure, prior CABG to the target vessel, acute MI within 48 hours.

The main angiographic inclusion criteria was a target lesion present in the native epicardial coronary artery 2.5–4.0mm in diameter that can be covered by a single M'Sure-S stent with a

maximum length of 40mm. Lesions having severe calcification, tortuousity, presence of thrombus, bifurcation sites, involving left main coronary artery , saphenous vein grafts and those with LVEF <30% were excluded from the Study.

M'Sure-S Sirolimus-eluting Coronary Stent System

M'Sure-S uses a cobalt–chromium (L605) platform and has an ultra-low (59μm) strut thickness. M'Sure-S has an intelligent cell design that allows maintaining a high radial strength with excellent flexibility. The stent is pre-mounted on a CE approved delivery system. The cytostatic, antiproliferative drug Sirolimus along with biocompatible and biodegradable polymers (PLLA & PLGA) is coated on entire stent length maintaining a 2μm thickness. The drug is timed to elute over a period of 28 to 30 days time, while the polymeric mixture degrades via hydrolysis and is eventually eliminated via the Krebs cycle as carbon dioxide and water. The stent has been sufficiently studied in porcine coronary artery and rabbit iliac models for its preclinical safety and efficacy to have been established.

Study Procedures

Each patient was treated by routine angioplasty procedure. M'Sure-S was deployed once visual estimation of the vessel diameter and lesion characterization had been undertaken, always keeping in mind the angiographic inclusion and exclusion criteria. At the end of the stent implantation, it was left to the interventional cardiologist's discretion whether or not to further treat the patient with a post-dilatation balloon catheter. Dual antiplatelet therapy (aspirin plus clopidogrel) was continued for up to one year post-procedure. Procedural success was defined as a successful device implantation with a residual stenosis of <20% of the vessel diameter, event-free sheath removal and subsequent discharge from the hospital. Table no. 1 provides baseline demographics and treatment details

Follow-up

Patients were followed up for 30 days and six months. The six month follow up was planned as an angiographic follow up using quantitative coronary angiographic (QCA) method.

Quantitative Coronary Angiographic Evaluation

The QCA were obtained at three distinct time-points – pre-stenting, post-stenting and at six month follow-up. All the CDs and the copies of CRFs were sent to an independent core laboratory Fact-Medis. QCA was performed using leading software and edge-detection techniques. The advanced understanding of the experts was used to characterize the lesions. In-stent and in-segment morphologies were measured. The target lesion was defined as the stented segment that could clearly be seen on the software. The 5mm segments immediately pre- and post-stented length were considered to be the in-segment portion.

Study End-points

The primary Safety endpoint of the Study is defined as Major Adverse Cardiac Events (MACE) at 30 days, defined as a composite of Death, MI (both Q-wave and Non Q-wave MI), Emergent CABG, or clinically driven TLR (repeat PCI or CABG), The primary Efficacy endpoint is the In-Stent and In-Segment Late Loss at 6-month follow-up determined by off-line QCA at the Core Lab.

The secondary Efficacy endpoints are, Angiographic/Device Success, Procedural Success, QCA derived vessel parameters in-stent and 5 mm proximal and 5 mm distal from the edge of the stent (Acute Gain, MLD, Diameter Stenosis, Late Loss, Binary Restenosis, In-stent MLD pre-, post and at 6-month follow-up).

Results

Characteristics of the Patients between December 2011 and August 2012, 32 patients who met the eligibility criteria were treated with 33 M'Sure-S stent (Patient no. 7 received 2 M'Sure-S stents). All patients were Indian in origin and belonged to the Asian race. Overall, 93.7% patients were male, with a mean age of 57.5 ± 9.7 years. A high prevalence of diabetes (21.88%), Hyperlipidemia (25%) and hypertension (50%) were noted in these patients. All patients presented with acute coronary syndrome, 6 patients (18.75%) had Stable Angina, 7 patients (21.88%) had Unstable Angina and 19 patients (59.37%) had an MI. Among all the treated patients 68.75% were Smoker and 43.75% patients had a Family History of Coronary Artery Disease.

The target lesion site was the left anterior descending coronary artery in 50% of cases and the right coronary artery in 25% of cases. Left circumflex artery disease was seen in 15.63% of patients. Lesions in the remaining patients involved the right obtuse marginal artery, which accounted for 3.13% of cases. 18.75% of patients presented with TIMI 0 flow, 46.88% TIMI I and 34.38% TIMI II Flow. 46.88% of patients had lesion classification of type B1 and B2 (with type B1 lesion dominating in 37.50% of the treatment settings). 25.01% of mild to moderate calcification patients were treated.

Procedural Characteristics

The maximum stent diameters used were 2.75 mm and 3.00 mm (both 36.36%) in 72.72% of the cases. Average stented diameter was 2.93 ± 0.30 mm and the average stented length was 20.12 ± 4.56 mm.

All patients successfully received M'Sure-S stent. Physician experience of stent acute performance, such as stent trackability, deliverability and radio-opacity, was found to be satisfactory. All patients were de-sheathed and subsequently discharged without any procedural event. Table no. 1 provides post-procedure baseline demographics.

Quantitative Coronary Angiography

Data on angiographic follow-up data at six months are available for 27 (84.38%) out of the 32 patients treated. The interim analysis provided by the core laboratory demonstrates an excellent in-stent late lumen loss of 0.05 mm and an in-segment late lumen loss of 0.05 mm. These results compare

favorably with those of currently available DES studies. As can be seen in Table no. 1, the median lesion length was 19.92 mm. Median reference vessel diameter was found to be 2.35 mm and minimum luminal diameter (MLD) was 0.98 mm. Median diameter stenosis was 79.29 % in these patients. Post-procedure QCA details are given in Table no. 1. Post-procedure in-stent MLD was 2.32 mm and residual diameter stenosis was maintained at a median of 13.26 %. In-stent acute gain was measured to be 1.34 mm. In-segment analysis revealed a MLD of 2.32 mm and a residual diameter stenosis of 24.56 %, with an acute gain of 1.34 mm. The six month angiographic follow-up data from 27 patients were studied and an interesting set of values are available in Table no. 1. Median in-stent MLD was found to be 2.30 mm, with a diameter stenosis of 11.26 % and a late lumen loss of 0.05 mm. interestingly, binary restenosis was not found in any patients and this remained 0% at the end of six months, thereby indicating high efficacy. Likewise median in-segment MLD was 2.35 mm and thus the late loss was calculated as 0.05 mm, with no binary restenosis.

Major Adverse Cardiac Events and Stent Thrombosis

All patients completed the 30-day primary end-point and were followed up to six months with 0% MACE. Zero per cent stent thrombosis from acute to late phase follow-up was observed, demonstrating a high standard of safety. No other complications occurred during this time frame, demonstrating the high safety profile of this new generation of SES.

Discussion

The primary analysis was performed according the intention to treat principle. Descriptive statistics was performed for all relevant variables. Count variables were summarized by the count and the percentage. Continuous various variables were summarized by the mean, standard deviation, minimum and maximum. The event variables, such as MACE, were summarized as time-to-event variables, and presented using the Kaplan-Meier method. Chi-Square method was utilized with a power of 95% and significance level = 0.005 for measuring any difference.

Earlier, DES causing late Stent thrombosis had thick struts which acted as a barrier for early endothelialization. M'Sure-S has low strut thickness (59μm), promising early endothelialization thus reducing the risk of stent thrombosis to minimum. M'Sure-S has drug elution kinetics of 28 to 30 days and a polymer degradation that is short and well documented. M'Sure-S has been found to be safe and efficacious in preclinical models and in the primary safety and efficacy study.

Conclusion:

Thus far, the PRISM Pilot study has demonstrated no major adverse cardiac event (MACE). No cases of stent thrombosis or any other complications have been observed. In terms of its efficacy parameters, at six month angiographic follow-up, 0.05mm of in-stent medial late luminal loss has been observed. 0% binary restenosis has been recorded thus far. Analysis of above data demonstrates safety and efficacy profile of M'Sure-S, similar to that observed in closely monitored other published randomized trials. The main finding is a high safety profile, with 0% MACE, 0% stent thrombosis and 0% binary restenosis rates.

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Six month Follow-up Quantitative Coronary Angiographic Data (n=27)	
Reference vessel diameter (mm)	2.63
In-stent	
Minimum luminal diameter (mm)	2.3
Percentage diameter stenosis	11.26
Late lumen loss (mm)	0.05
Binary restenosis, % (n)	0
In-segment	
Minimum luminal diameter (mm)	2.35
Percentage diameter stenosis	21.14
Late lumen loss (mm)	0.05
Binary restenosis, % (n)	0

Post-procedure Quantitative Coronary Angiographic Data (n=27)	
Reference vessel diameter (mm)	2.67
In-stent	
Minimum luminal diameter (mm)	2.32
Percentage diameter stenosis	13.26
Acute gain (mm)	1.34
In-segment	
Minimum luminal diameter (mm)	2.32
Percentage diameter stenosis	24.56
Acute gain (mm)	1.34