International Journal of Cardiology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Oral sirolimus: A possible treatment for refractory angina pectoris in the elderly

Alexandru Mischie [a], Sylvain Chanseaume [a], Philippe Gaspard [a], Catalina Liliana Andrei [b], Crina Sinescu [b], Michele Schiariti [c,*]

[a] Invasive Cardiology Unit, Centre Hospitalier de Montluçon, 18 Avenue du 8 Mai 1945, 03100 Montluçon, France
[b] Carol Davila University of Medecine, 37 Dionisie Lupu, 1st District, 020022 Bucharest, Romania
[c] Department of Cardiovascular Sciences, Sapienza University of Rome, Viale del Policlinico 155, 00161 Rome, Italy

ARTICLE INFO

Article history:
Received 21 July 2016
Accepted 28 July 2016
Available online xxxx

Keywords:
Sirolimus
Refractory angina
Survival
Stents
CAD

ABSTRACT

Refractory angina pectoris (RAP) is a clinical problem, frequently encountered in the elderly, associated with high health-care costs. Until recently, the goal of RAP treatment aimed at improving the quality of life (QoL) because it was thought that mortality rates were not different between stable angina pectoris and RAP. Our purpose was at determining whether any mortality rate difference exists and whether any novel therapeutical solution might be translated into clinical practice. We therefore performed a literature review to assess current optimal treatment of RAP patients, including all studies involving the use of oral sirolimus and stents, although no consistent evidence was found for any specific treatment to improve survival, apart from minor QoL amelioration. A large mortality difference was seen between RAP and stable angina pectoris. On the other hand, therapeutic approaches to RAP patients showed frequent complications and several contraindications, depending on the procedure.

We propose to inhibit instead of stimulating angiogenesis, by giving oral sirolimus, an immunosuppressive drug, thereby decreasing the atherosclerotic process and its evolution. Sirolimus was shown to decrease left ventricular mass (thus indirectly decreasing myocardial oxygen needs and consumption). It might stop and, in some cases, even enable regression of plaque progression. Sirolimus side effects are mild to moderate and wash-out rapidly at treatment discontinuation. Compared with current therapies sirolimus treatment is more health-care cost efficient. It should be important to design a trial in RAP patients powered to reduce mortality and QoL increase.

1. Introduction

Refractory angina pectoris (RAP) is defined by angiographic confirmation of coronary artery disease (CAD), proof of an ischemic myocardial territory and severe stable angina pectoris (Canadian Cardiovascular Society class 3 or 4) not accessible to either percutaneous coronary interventions (PCI) or coronary artery by-pass graft (CABG) and the absence of other causes of chest pain [1,2]. It is a condition quite frequently seen in the elderly [1–3]. Until recently, the goal of RAP treatment was aimed at improving the quality of life (QoL) because it was erroneously thought that the mortality rates do not differ between angina pectoris (AP) and RAP. However, a Literature review shows that mortality almost doubles. Current guidelines [1,2] are old and shallow in evaluating the real mortality rates of RAP, either by omission or because available studies are difficult to compare. Moreover, most of the interventions for the treatment of RAP have a limited/slightly superior result for symptom's regression and no effect to decrease mortality.

RAP is a pathophysiological entity with considerable public health effects. Between 5 and 15% of patients presenting angina should be considered as having RAP, as reported by Mannheimer et al. [1]. The Third National Health and Nutrition Examination Survey concluded that in the United States 300,000 to 900,000 individuals have RAP,

Abbreviations: RAP, refractory angina pectoris; CAD, coronary artery disease; PCI, percutaneous coronary interventions; CABG, coronary artery by-pass graft; QoL, quality of life; AP, angina pectoris; SCS, spinal cord stimulation; EECP, enhanced external counter-pulsation; SWT, shock wave therapy; TENS, transcutaneous electrical nerve stimulation; LV, left ventricle; OS, oral sirolimus; BMS, bare metal stent; LLL, late luminal loss; IVUS, intravascular ultrasound; TLR, target lesion revascularization; TVR, target vessel revascularization; DES, drug-eluting stents.

* Corresponding author at: Department of Cardiovascular, Respiratory, Nephrological, Anesthesiological and Geriatrical Sciences, Sapienza University of Rome, Viale del Policlinico, 155, Roma 00161, Italy.
E-mail addresses: alexandru_mischie@yahoo.com (A. Mischie), s.chanseaume@ch-montlucon.fr (S. Chanseaume), p.gaspard@ch-montlucon.fr (P. Gaspard), ccatalina97@yahoo.com (C.L. Andrei), crinasinescu@gmail.com (C. Sinescu), michele.schiariti@uniroma1.it (M. Schiariti).

http://dx.doi.org/10.1016/j.ijcard.2016.07.206
0167-5273/

Table 1
Oral sirolimus and stents in non-randomized controlled clinical trials.

Author/Method	Year of publication	Groups	No. of patients	Loading dose/daily dose	Median follow-up period	TVR %	TLR %	Death/cardiac death %
Waksman et al. [41]	2004 De novo stenosis	OS low dose plus BMS	30	5 mg immediately before or after BMS then 2 mg/day for 30 days	6 months	16.7	14.3	0.0
		OS high dose plus BMS	30	5 mg immediately before or after BMS then 5 mg/day for 30 days		20.6	6.9	0/0
Rodriguez et al. [42,43]	2003 and 2005 Pilot study	OS plus BMS (sirolimus blood levels <8 ng/ml)	34	6 mg after BMS then 2 mg/d for 28 days	6.8 +/− 1.2 months	NA	18.4	0.0
		OS plus dultiazem plus BMS (sirolimus blood levels >8 ng/ml)	42	6 mg after BMS then 2 mg/d plus diltiazem 180 mg/day for 28 days		NA		0/0
Brara et al. [40]	2003 Pilot study Recalcitrant restenosis	PTCA for recalcitrant restenosis, 90.9% had coronary radiation failure.	22	6 mg after PTCA then 2 mg/d for 30 days	9.9 +/− 1.8 months (clinically driven coronarography in 68.2% of patients)	53.6%	59.1	0/0

Abbreviations: OS-oral sirolimus; SR-slow release; BMS-bare metal stents; PTCA-percutaneous transluminal coronary angioplasty; NA-non-available; LLL-late luminal loss; TLR-target lesion revascularisation; TVR-target vessel revascularisation; MACE-major adverse cardiac events; LVEF-left ventricular ejection fraction.

corresponding to new annual diagnosed cases between 25,000 and 75,000 [3]. Another report [4] stated that 1000–2000 new RAP cases are being treated each year in a hospital located in Beijing and that the percentage of diffuse triple-vessel disease patients that continue to have RAP despite current treatments is around 20–30%.

In a subgroup with confirmed coronary disease [5], a 2.3% patient-years rate of death and myocardial infarction have been noted in a stable angina population. In addition, several authors have reported different data from various studies at different follow-up intervals: a 4.6% death rate/year at 2 years of follow-up in some reports [6,7] and a 0.9–1.4% death rate/year in other reports [8–13]. A recent meta-analysis [14] reported an 8.7% death rate at 4.2 years, which represents roughly a 2% death rate/year. The COURAGE study reported a 4.2% death rate/year at 4.6 years of follow-up [15]. The STAR registry in Germany showed a 18.4% mortality at 5 years (3.6% death rate/year) in the general population and a 29% death rate for diabetics at 5 years. The IONA study [16] reported a mortality of 4.3% in the nicorandil-treated group vs. 5% in the placebo group at 1.6 years and thus a rate of death of 2.6%/year at 1.6 years of follow-up, but not all patients had severe angina and maximal treatment.

The ESBY trial [spinal cord stimulation (SCS) vs. CABG] showed a 27.9% mortality at 5 years of follow-up (5.58% death rate/year) and also proved that survival was similar between the groups [17]. The suggestion of a mortality of up to 16.9% at one year [18] is often quoted. Rück et al. [19] selected 150 RAP patients and a mean age of 63 years and found a mortality of 5.5% at one year and 13.5% at 3 years (4.5% deaths/year). The most important information about the prognosis of RAP comes from a recent report that found a fatality rate in RAP patients at one year of 10% and in a control group (patients accepted for revascularization due to severe angina) of 0.7% ($p < 0.001$) [20].

2. Treatment of RAP

The current interventions in refractory angina have some effect in abolishing pain and symptoms, but they are not free from complications. Most treatment options encourage angiogenesis and include enhanced external counterpulsation (EECP), shock wave therapy (SWT), growth factors and gene therapy, with or without antiplatelets' agents, based on the idea that fighting against slow coronary flow might be effective therapeutically [21–25]. However, most of these treatments generally result in minor improvements in the functional status. Other treatment options include transcutaneous electrical nerve stimulation (TENS) and SCS but remain essentially experimental. Current guidelines [1,2] and meta-analyses [26,27] summarize the minor effect on QoL of these interventions with no difference in mortality. The RAP patients also have numerous contraindications that limit the use of these treatments. There are contraindications for EECP: severe vascular disease (lower limbs, aortic aneurysm), bleeding disorders, acute/sub-acute heart failure, different arrhythmias (the devices are ECG-synchronized), acute or sub-acute thrombotic venous disease, pregnancy, uncontrolled systemic hypertension, severe aortic insufficiency and anticoagulant therapy and bleeding disorders or being treated by anticoagulant therapy. There are also contraindications for SWT: cardiac pacemakers and patients with local infections, pregnancy, malignancy, severe valvular heart disease, active endocarditis, myocarditis or pericarditis, severe pulmonary disease, intraventricular thrombus and acute myocardial infarction occurred <3 months previously. All of these treatments have mildly increased device-related complications, with SCS having the highest rate; in the largest series of SCS implantations for failed back surgery syndrome (PROCESS trial), device-related complications were reported in 32% of patients at 12 months.

Interventions such as thoracic epidural anesthesia, left stellate ganglion blockade, laser revascularization (percutaneous or transmyocardial) and endoscopic thoracic sympathectomy, showed high rates of complications or death and are no longer used.

3. Sirolimus effects on the heart

Sirolimus is an antibiotic from the macrolide class. Its pharmacological behavior is characterized by inhibiting the proliferation and migration of smooth muscle cells in the vessels. This is done by binding to the cytosolic receptor FKBP12 and by inhibiting the downregulation of the cyclin-dependent kinase inhibitor p27kip1. It possesses 2 primary cardiovascular effects:

3.1. Decreasing cardiac mass

In the heart, sirolimus inhibits the mammalian-target-of-rapamycin protein. Pressure overload results in ventricular hypertrophy by

Please cite this article as: A. Mischie, et al., Oral sirolimus: A possible treatment for refractory angina pectoris in the elderly, Int J Cardiol (2016), http://dx.doi.org/10.1016/j.ijcard.2016.07.206

In stent restenosis (%)/LLL	MACE %	Discontinued medication %	Diabetes mellitus %	LVEF	Reference diameter/ *lesion lenght*	No. of lesions	Type of lesion	Conclusions
7.1/0.6 +/− 0.54	24 (TLR included)	10	13	54 +/− 10%	3.00 +/− 0.44/14.12 +/ −6.75	49	NA	OS for the prevention of restenosis is safe, feasible, and associated with low rates of repeat revascularization. No correlation between the dose sirolimus dose and restenosis.
6.9/0.71 +/− 0.49	20 (TLR included)	30.33	23	51 +/− 6%	3.09 +/− 0.51/13.57 +/ −4.84	37	NA	
22%/1.10	20 (TVR and TLR included)	3.9 (one patient in the low group serum sirolimus and 2 âtients	31	NA	3.15/10.7	49 (24.5% were intra-stent restenosis)	A: 18% B1:29% B2: 27% C: 27%	Higher sirolimus blood levels at 3 weeks (>8 ng/ml) were associated with a lower rate of angiographic restenosis and LLL. Good tolerability.
6.2%/0.60		in the high group serum sirolimus.	11.3	NA	3.00/10.2	54	A: 14% B1:26% B2: 29% C: 31%	
86.7%/NA	0 (TVR and TLR not included)	50%	40.9	NA	NA/NA	28	NA	No benefit for patients with recalcitrant restenosis. No difference between those who discountinued treatment and those with full-dose treatment.

increased synthesis of intracellular protein; this process is regulated by the mammalian-target-of-rapamycin protein. Protein inhibition (especially the ribosomal protein S6) was noted when sirolimus was administered to mice subjected to cardiac pressure overload, resulting in a 50% decrease in myocardial cell growth compared with the control group [28,29]. In an animal model, sirolimus reduced cardiomyocyte growth and reversed inter-myocardiocytic fibrosis [30], which improved cardiac remodeling. Observational studies in humans concluded that left ventricular mass is being reduced in a significant manner when switching from a calcineurin inhibitor to sirolimus [31,32].

3.2. Inhibiting atherosclerosis

We should keep in mind that cardiac allograft vasculopathy, defined as intimal thickening of the arteries found in heart transplant recipients (resulting from smooth muscle proliferation) has a distinct pathophysiology in comparison to CAD. All studies discussed below do not involve cardiac allograft vasculopathy. In apolipoprotein E mice knock-out models (a well-accepted model of cardiovascular disease), the administration of sirolimus was able to decrease the atherosclerotic plaques growth significantly in more than 50% of the cases and to also inhibit interleukins, despite the high circulating lipid levels [33,34]. When inflammation and hyperlipidemia are present, sirolimus proved its anti-atherosclerotic effect through reduced accumulation of intracellular cholesterol, abolished inflammatory response and synthesis of pro-atherogenic cytokines [34,35]. Everolimus was used to inhibit atherosclerosis in mice with deficiency in low-density lipoprotein receptors, despite severe hypercholesterolemia, in a study by Mueller et al. [36]; reduction of inflammatory cell mediators (interleukin-12p40, interleukin-5 and interleukin-1) and delayed transition from early macrophage-enriched lesions to advanced atherosclerotic plaques were observed.

In renal transplant recipients, lower homocysteine levels were correlated with everolimus use [37]. Mammalian-target-of-rapamycin protein inhibitors blocked basal interleukin-6 secretion by 45% and inhibited cell proliferation in a human coronary artery-endothelial cell research model [38]. In transplanted patients, everolimus induced a diminished intima proliferation (29% vs. 81%) in comparison with the untreated controls. Strikingly, the combining of everolimus and clopidogrel nearly abolished the atherosclerotic process (intima proliferation: 11% vs. 81%) [39].

4. Oral sirolimus (OS) and stents

Non-randomized controlled trials are detailed in Table 1 [40–43]. The Orbit trial [41] found that major adverse cardiac events (20% vs. 24%) favored the high dose OS group at 6 months. The complete ORAR study [42] included a pilot-first phase study [43] that enrolled 34 patients who were administered a 6 mg OS loading dose after bare metal stent (BMS) implantation, followed by 2 mg/d for 28 days (low-OS blood level group), and a phase II study that enrolled 42 patients with a 6 mg OS loading dose after BMS implantation, followed by 2 mg/day OS plus 180 mg/day diltiazem for 28 days (high-OS blood level group). The last pilot trial of OS [44] was not included in Table 1 because of the low number of enrolled patients (12 patients with high risk for intra-stent restenosis, including 8 intra-stent restenotic lesions). They treated patients with 15 mg OS loading dose given one day before the procedure, followed by 5 mg every day for 28 days (blood levels were measured every week). A high blood level of sirolimus was targeted (10–15 ng/ml). An overall good tolerance of sirolimus was observed (however one death was noted). Follow-up performed at 4- and 8-months showed angiographic late luminal losses (LLL) of 0.40 ± 0.24 and 0.67 ± 0.45 mm ($P < 0.01$) and intravascular ultrasound (IVUS) intra-stent relative volumetric obstructions of 14.4 ± 9.1% and 23.2 ± 10.1% ($P < 0.01$), respectively. At the 24-month clinical follow-up study adverse events consisted of one death (8.3%), two (11.1%) target lesion revascularizations (TLR), and four (22.2%) target vessel revascularizations (TVR).

There are 3 randomized controlled trials that investigated the correlation between OS, stents and restenosis (Table 2) [45–47]. In the OSIRIS trial, there was no significant difference regarding newly diagnosed malignancies, TVR and death between the high-dose/low-dose sirolimus and the placebo groups at 4 years of follow-up [45,48]. In the ORAR II trial [46], sirolimus blood levels at baseline were 13.4 ± 4.5 ng/ml, minor side effects were observed in 26% of the patients, and 4% of the patients discontinued medication. Minor changes in leucocytes' and triglycerides' counts returned to normal after OS cessation. This trial clearly showed that OS plus BMS strategy reached the angiographic effect of a 1st-generation drug-eluting stent (DES),

Please cite this article as: A. Mischie, et al., Oral sirolimus: A possible treatment for refractory angina pectoris in the elderly, Int J Cardiol (2016), http://dx.doi.org/10.1016/j.ijcard.2016.07.206

Table 2
Oral sirolimus and stents in randomized controlled clinical trials.

Author/Method	Year of publication	Groups	No. of patients	Loading dose/daily dose	End-point Median FU period	TVR %	TLR %	Death/cardiac death %
Rodriguez et al. [47]	2009 De novo stenosis	OS plus BMS	100	10 mg one day before then 3 mg/day plus diltiazem SR 180 mg/day for 14 days	18.3 +/− 7 months	10.6	7.0	3.0/1.0
		DES	100	No OS		10.5	8.2	7.0/4.0
Rodriguez et al. [46]	2006 De novo stenosis	OS plus BMS	50	6 mg at 2.7 h before stent then 3 mg/day plus diltiazem SR 180 mg/day for 14 days	Restenosis and LLL @ 9 months. TVR, TLR and MACE @ 1 year	8.3	7.6	4.0/1.0
		BMS	50	No OS		38	37.2	4.0/2.0
Hausleiter et al. [45]	2004 Intra-stent restenosis	Placebo plus BMS	102	Placebo oral therapy	6 months angiographic and 1 year clinical	25.5%	NA	0/0
		OS low dose plus BMS	99	6 mg 1 day before BMS then 2 mg/d for 8 days		24.2%	NA	3/1
		OS high dose plus BMS	99	12 mg 2 days before BMS, 8 mg 1 day before BMS, 4 mg the day of intervention then 2 mg/d for 7 days		15.2%	NA	2/1

Abbreviation: OS-oral sirolimus; BMS-bare metal stent; DES-drug-eluting stents; SR-slow release; FU-follow-up; LLL-late luminal loss; TLR-target lesion revascularisation; TVR-target vessel revascularisation; MACE-major adverse cardiac events; NA-non-available; LVEF-left ventricular ejection fraction; PCI-percutaneous coronary intervention.

with minor side effects. In the ORAR III trial [47] OS plus BMS strategy was more cost-effective than DES strategy (18 months of follow-up). Similar angiographic outcomes were found and a trend showing lower major adverse cardiac events rates (9% vs.15%) and death rates (3% vs. 7%) in favor of the OS plus BMS group. Sirolimus blood levels were not measured.

Table 3
Adverse effects of oral sirolimus and stents.

Author	Number of patients on OS	Loading dose/daily dose	Timing of exams during follow-up	Discontinued medication	AE (%)	Sirolimus blood levels (ng/ml)	Gum sores	Diarrhoea
Rodriguez et al. [47]	100	10 mg one day before then 3 mg/day plus diltiazem SR 180 mg/day for 14 days	Baseline, 7 and 30 days plus regular interviews	4%	24%	NA	14%	12%
Rodriguez et al. [46]	50	6 mg at 2.7 h before stent then 3 mg/day plus diltiazem SR 180 mg/day for 14 days	Baseline, 7, 14 and 21 days plus regular interviews	4%	26%	13.46 +/− 4.5 at baseline	16%	6%
Waksman et al. [41]	30	5 mg immediately before or after BMS then 2 mg/day for 30 days	Baseline, 30 days and 6 months.	10%	43.3%	5.3 +/− 3.1 at day one, 6.4 +/− 4.2 at 30 days	13.3%	16.6%
	30	5 mg immediately before or after BMS then 5 mg/day for 30 days		30.33%	66.7%	6.4 +/− 6.4 at day one, 18.7 +/− 12.7 at 30 days	20%	20%
Hausleiter et al. [45]	99	6 mg 1 day before BMS then 2 mg/d for 8 days	Day of procedure, third day after procedure and at 6 months.	3%	3%	10.0 +/− 8.5 day of the procedure, 6.6 +/− 4.9 at day 3 afterwards	NA	NA
	99	12 mg 2 days before BMS, 8 mg 1 day before BMS, 4 mg the day of intervention then 2 mg/d for 7 days		4%	4%	18.1 +/− 5.2 day of the procedure, 10.5 +/− 5.0 at day 3 afterwards	NA	1
Brara et al. [40]	22	6 mg after PTCA then 2 mg/d for 30 days	Baseline, 1, 3 and 5 w after intervention	50% (treatment duration of 14.5 +/− 6.5 days)	50%	Not done	4.5%	NA
Rodriguez et al. [42,43]	76	6 mg after BMS then 2 mg/d (plus or minis diltiazem 180 mg/day) for 30 days	Baseline, 1, 3 and 4 w after intervention	3.9%	25%	@ 3 weeks	5.2	7.8

Abbreviations: OS-oral sirolimus; SR-slow release; BMS-bare metal stents; PTCA-percutaneous transluminal coronary angioplasty; AE-adverse effects; NA-non-available.

Please cite this article as: A. Mischie, et al., Oral sirolimus: A possible treatment for refractory angina pectoris in the elderly, Int J Cardiol (2016), http://dx.doi.org/10.1016/j.ijcard.2016.07.206

In stent restenosis (%)/LLL	MACE %	Discontinued medication %	Diabetes mellitus %	LVEF	Reference diameter/ *lesion lenght stent length*	No. of lesions	Type of lesion	Conclusions
7.2%/NA	9% (TVR and TLR not included)	4	24	<40% in 11%	2.8 +/− 0.5 from which 36.1% < 2.5 mm/13.8 +/− 5.5 from which 29.7 > 18 mm	158	A + B1: 38.8% B2 + C: 61.2%	OS plus BMS is cost saving compared to DES in patients undergoing PCI for *de novo* coronary lesions. Similar outcomes were found between the 2 groups.
6.4%/NA	15% (TVR and TLR not included)	NA	33	<40% in 6%	2.8 +/− 0.4 from which 28.2% < 2.5 mm/ 14.4 +/− 5.9 fom which 35.3 > 18 mm	170	A + B1: 32.3% B2 + C: 67.8%	
11.6%/0.73 +/− 0.40	20% (TVR included)	4	24	NA	2.96 +/− 0.64/13.35 +/− 6.33	66	A: 4.5% B1:25.7% B2: 46.9% C: 22.7%	OS significantly reduces angiographical and clinical parameters of restenosis.
36.4%/1.41 +/− 0.67	44% (TVR⋯included)	NA	8	NA	2.91 +/− 0.41/12.79 +/− 4.28	59	A: 5% B1:35.5% B2: 39% C: 20.3%	
42.2%/0.60 +/− 0.56	2% (30 days) 27.5% (1 year, including TVR)	0	27.5	55.7 +/− 12.1	2.61 +/− 0.53/NA	NA	NA	Significant reduction of angiographic restenosis after treatment of intra-stent restenosis with OS and BMS. Correlation sirolimus blood level at the time of intervention with LLL at FU.
38.6%/0.72 +/− 0.70	3% (30 days) 29.3% (1 year, including TVR)	3	27.3	55.4 +/− 12.8	2.60 +/− 0.48/NA	NA	NA	
22.1%/0.49 +/− 0.54	2% (30 days) 18.2% at 1 year (including TVR)	4	32.2	55.2 +/− 14.0	2.57 +/− 0.53/NA	NA	NA	

Constipation	Gastritis	Rash	Fever	Psoriasis	Angioedema	Nausea and vomiting	Triglyceride increase but normalized at FU	Leucopenia % (normalized at follow-up)	Mild hepatic dysfunction (normalized at follow-up)	Other
4%	1%	3%	5%	1%	1%	NA	NA	Decrease by 5.4%	NA	NA
0%	0%	2%	0%	NA	2%	0%	Increase by 23%	Decrease by 32.5%	NA	NA
NA	NA	6.6%	NA	NA	NA	6.6%	0%	0%	0%	0%
NA	NA	36.6%	NA	NA	NA	3.3%	Severe increase in3.3%	Severe decrease in 6.6% patients	3.3%	3.3% (fatigue(
NA	NA	NA	NA	NA	NA	1%	NA	Decreased by 8.6%	NA	1% (infections) 1% (Hemoglobin drop)
NA	NA	NA	NA	NA	2 (suspected allergy)	NA	NA	Decreased by 22%	NA	1% (infections)
NA	NA	NA	4.5%	NA	NA	NA	13.6%	13.6%	4.5%	4.5% (acnea)
2.6	1.3	9.2	2.6	NA	NA	1.3	NA	Negative	NA	1.3% (headeache), 1.3% (insomnia)

Please cite this article as: A. Mischie, et al., Oral sirolimus: A possible treatment for refractory angina pectoris in the elderly, Int J Cardiol (2016), http://dx.doi.org/10.1016/j.ijcard.2016.07.206

5. Sirolimus in transplant recipients

When sirolimus was administered to *de novo* heart transplant patients, it reduced the progression of cardiac allograft vasculopathy, decreased acute rejection and prevented CAD at 6 months and 2 years. IVUS showed that in sirolimus-treated patients, there was no progression in the intima and media, and significant protection against luminal encroachment [49]. Sirolimus was also shown to regress cardiac hypertrophy in patients having had a heart or kidney transplant [32,50].

6. Adverse effects

The side effects of OS in the stented patients were minor to moderate (Table 3). In one study [42,43], the side effects (identified in 25% of the cases) had a minimal impact on the discontinuation rate (3.9% of the overall population), and 90% of the side effects occurred within the first week of treatment. Taking the two largest trials of OS [45,47], the discontinuation rate was 3–4% of patients, and the adverse effects varied between 7% and 24%. The most frequent adverse effects were gum sores (14%), diarrhea (12%), fever (5%), constipation (4%) and rash (3%). Other noted adverse effects were gastritis, psoriasis, angioedema, nausea and vomiting, each appearing in 1% of the patients. Leucocytes decreased from 5.5% to 22% of the baseline values but returned to normal after treatment discontinuation. Normalizations of triglycerides, cholesterol and hepatic markers were also observed after stopping treatment. Overall, OS was a safe and well-tolerated therapy. In transplanted patients, these changes are larger and appear more frequently and may include higher levels of LDL cholesterol, hyperlipidemia with hypertriglyceridemia, neutropenia, anemia and thrombocytopenia [51–53].

7. Therapeutic blood levels

7.1. In OS-stented patients

In the Orbit trial [41], sirolimus blood levels (ng/ml) were 5.3 ± 3.1 on day one and 6.4 ± 4.2 at 30 days for the low dose group and 6.4 ± −6.4 on day one and 18.7 ± 12.7 at 30 days for the high dose group. In the ORAR study [42,43], sirolimus blood levels were measured at 3 weeks. Diltiazem was added because lower sirolimus side effects rates and higher therapeutic blood levels of sirolimus were observed when the latter was used; patients that presented restenosis had a mean sirolimus blood concentration of 7.9 ng/ml. In the OSIRIS trial [45], sirolimus blood levels (ng/ml) were 10.0 ± 8.5 and 18.1 ± 5.2 on the day of the procedure and 6.6 ± 4.9 and 10.5 ± 5.0 on the third day after the procedure in the low- and high-dose sirolimus groups, respectively.

7.2. In transplanted patients

The 2010 Guidelines for the Care of Heart Transplant Recipients Task Force [51] indicated the cut-offs for therapeutic drug monitoring of sirolimus and everolimus: between 3 and 8 ng/ml for everolimus (when used in combination with cyclosporine) and between 4 and 12 ng/ml for sirolimus, measured at least 5 days after adjusting the dose when a new steady state is achieved. Diltiazem was added to sirolimus because lower rates of side effects and higher therapeutic blood levels of sirolimus were observed in renal transplanted recipients [52,53]. Optimal immunosuppressive sirolimus levels were reached after 4 days of oral administration [53]. Attention should also be given to the drug interactions as they could increase or decrease sirolimus blood levels [51].

8. Implications and future directions

8.1. For patients

In our opinion and considering the new data regarding mortality rates, the treatment options for RAP should aim at decreasing the incidence of cardiovascular death besides an increase in the QoL. OS could be an effective solution. When drafting a trial design, important outcomes such as data showing that the atherosclerotic plaque has possibly regressed, stopped growing or grows at a much slower rate under sirolimus treatment (evaluation by IVUS) should be included. If available, magnetic resonance imaging would bring essential information about left ventricular mass, function, perfusion and volumes at rest and under stress.

Given that a recent study found that the fatality rate in RAP patients at one year was 10% [20] and considering a mean death rate of patients with stable AP of 2% [14], 270 RAP patients should be enrolled in order to detect an absolute 8% drop from 10% in the control group to an estimated 2% in the OS group for the primary outcome with 5% significance and 80% power. Allowing for 3% cross-over/non-compliance in the control group and 3% cross-over/non-compliance in the experimental group, a total of 306 patients are required.

The active period of treatment with sirolimus should be 3 to 6 months but also possibly more. Should this treatment be intermittent, and how long should the "off" cycle be? Given that sirolimus has mild to moderate adverse effects, a treatment period of no more than 6 months would likely minimize the risks. In addition, this treatment should most likely be repeated each year. The total study duration should also be defined.

8.2. For health-care cost reduction

RAP patients are fragile and present to the emergency room every time chest pain appear which does not respond to drugs (thus translating into at least 6 h of cardiac enzyme monitoring in a hospital setting). Although sirolimus cost for one month of treatment rises to 1,000 Euros, it could be an efficient treatment regarding health-care costs because only one day of hospital admission in Western countries costs approximately 1,400 Euros. The total OS treatment cost at 6 months/year would be approximately 13,000 Euros after 2 years. For comparison purposes, the ESBY trial [17] reported at 2 years of follow-up the overall health-care utilization and costs and concluded that the mean hospitalization duration was higher in patients receiving CABG (mean duration of 11.1 days, $P < 0.0001$) than in patients receiving SCS (mean duration of 5.0 days). When all costs were considered (the follow-up treatments and visits, hospital days and the cost of the primary intervention), the health-care costs were in favor of the SCS arm (16,400 Euros) vs. 18,800 Euros for each CABG patient ($P < 0.01$).

9. Conclusions

Whatever the future treatments for RAP, their potential for inherent complications should be considered. Coronary microvascular dysfunction is highly prevalent in women with chest pain and may explain a greater incidence of refractory angina in women [54]. Because there is an important difference in mortality compared with patients with stable AP, treatment in RAP should focus mainly on cardiovascular death reduction. OS appears to be an attractive option because its non-invasiveness and because of the overall ineffectiveness of other therapies. Whatever the treatment strategy, it must be weighed against the therapeutic positive/negative potential and data concerning the natural course of the disease. Additionally, the "refractory" aspect of angina ought to be assessed regularly as a small number of patients become amenable to "standard" treatment (PCI/CABG).

Please cite this article as: A. Mischie, et al., Oral sirolimus: A possible treatment for refractory angina pectoris in the elderly, Int J Cardiol (2016), http://dx.doi.org/10.1016/j.ijcard.2016.07.206

Acknowledgement and conflict of interest

The authors report no relationships that could be construed as a conflict of interest [55–57].

References

[1] C. Mannheimer, P. Camici, M.R. Chester, et al., The problem of chronic refractory angina; report from the ESC joint study group on the treatment of refractory angina, Eur. Heart J. 23 (2002) 355–370.
[2] M. McGillion, H.M. Arthur, A. Cook, et al., Management of patients with refractory angina: Canadian Cardiovascular Society/Canadian Pain Society joint guidelines, Can. J. Cardiol. 28 (2 Suppl.) (2012) S20–S41.
[3] National Center for Health Statistics, Plan and operation of the Third National Health and Nutrition Examination Survey, 1988–94. Series 1: programs and collection procedures, Vital Health Stat. 1 (32) (1994) 1–407.
[4] S. Wang, J. Cui, W. Peng, M. Lu, Intracoronary autologous $CD34^{+}$ stem cell therapy for intractable angina, Cardiology 117 (2010) 140–147.
[5] C. Daly, F. Clemens, J.L. Lopez-Sendon, et al., The impact of guideline compliant medical therapy on clinical outcome in patients with stable angina: findings from the Euro heart survey of stable angina, Eur. Heart J. 27 (2006) 1298–1304.
[6] W.B. Kannel, M. Feinleib, Natural history of angina pectoris in the Framingham study. Prognosis and survival, Am. J. Cardiol. 29 (1972) 154–163.
[7] J.M. Murabito, J.C. Evans, M.G. Larson, D. Levy, Prognosis after the onset of coronary heart disease. An investigation of differences in outcome between the sexes according to initial coronary disease presentation, Circulation 88 (1993) 2548–2555.
[8] S. Juul-Moller, N. Edvardsson, B. Jahnmatz, A. Rosen, S. Sorensen, R. Omblus, Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris. The Swedish Angina Pectoris Aspirin Trial (SAPAT) Group, Lancet 340 (1992) 1421–1425.
[9] H.J. Dargie, I. Ford, K.M. Fox, Total Ischaemic Burden European Trial (TIBET). Effects of ischaemia and treatment with atenolol, nifedipine SR and their combination on outcome in patients with chronic stable angina. The TIBET study group, Eur. Heart J. 17 (1996) 104–112.
[10] N. Rehnqvist, P. Hjemdahl, E. Billing, et al., Effects of metoprolol vs. verapamil in patients with stable angina pectoris. The Angina Prognosis Study in Stockholm (APSIS), Eur. Heart J. 17 (1996) 76–81.
[11] C.J. Pepine, E.M. Handberg, R.M. Cooper-DeHoff, et al., A calcium antagonist vs. a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial, JAMA 290 (2003) 2805–2816.
[12] R.A. Henderson, S.J. Pocock, T.C. Clayton, et al., 7 year outcome in the RITA-2 trial: coronary angioplasty versus medical therapy, J. Am. Coll. Cardiol. 42 (2003) 1161–1170.
[13] C. Brunelli, R. Cristofani, A. L'Abbate, Long-term survival in medically treated patients with ischaemic heart disease and prognostic importance of clinical and electrocardiographic data (the Italian CNR Multicentre Prospective Study OD1), Eur. Heart J. 10 (1989) 292–303.
[14] A. Schomig, J. Mehilli, A. de Waha, M. Seyfarth, J. Pache, A. Kastrati, A meta-analysis of 17 randomized trials of a percutaneous coronary intervention-based strategy in patients with stable coronary artery disease, J. Am. Coll. Cardiol. 52 (2008) 894–904.
[15] W.E. Boden, R.A. O'Rourke, K.K. Teo, et al., Optimal medical therapy with or without PCI for stable coronary disease, N. Engl. J. Med. 356 (2007) 1503–1516.
[16] IONA Study Group, Effect of nicorandil on coronary events in patients with stable angina: the Impact Of Nicorandil in Angina (IONA) randomised trial, Lancet 359 (2002) 1269–1275 (Erratum in: Lancet 2002;360:806).
[17] O. Ekre, T. Eliasson, H. Norrsell, P. Wahrborg, C. Mannheimer, Electrical stimulation versus coronary artery bypass surgery in severe angina pectoris. Long-term effects of spinal cord stimulation and coronary artery bypass grafting on quality of life and survival in the ESBY study, Eur. Heart J. 23 (2002) 1938–1945.
[18] D. Mukherjee, D.L. Bhatt, M.T. Roe, V. Patel, S.G. Ellis, Direct myocardial revascularisation and angiogenesis: how many patients may be eligible? Am. J. Cardiol. 84 (1999) 598–600.
[19] A. Rück, C. Sylvén, EUROINJECT ONE study group, Refractory angina pectoris carries a favourable prognosis: a three-year follow-up of 150 patients, Scand. Cardiovasc. J. 42 (2008) 291–294.
[20] P. Andréll, O. Ekre, L. Grip, P. Währborg, P. Albertsson, T. Eliasson, A. Jeppsson, C. Mannheimer, Fatality, morbidity and quality of life in patients with refractory angina pectoris, Int. J. Cardiol. 147 (2011) 377–382.
[21] E. Mangieri, G. Tanzilli, G. De Vincentis, F. Barillà, S. Remediani, M.C. Acconcia, C. Comito, C. Gaudio, F. Scopinaro, P.E. Puddu, G. Critelli, Slow coronary flow and stress myocardial perfusion imaging. Different patterns in acute patients, J. Cardiovasc. Med. 7 (2006) 322–327.
[22] E. Mangieri, G. Tanzilli, C. Greco, F. Pelliccia, P.E. Puddu, M.C. Acconcia, V. Paravati, C. Gaudio, Clinical results of two-year dual antiplatelet percutaneous coronary intervention with paclitaxel-eluting stents: a single centre study, EuroIntervention 2 (2007) 1–6.
[23] M. Schiariti, A. Saladini, B. Missiroli, F. Papalia, D. Cuturello, P.E. Puddu, C. Gaudio, Safety of downstream high-dose tirofiban bolus among 1578 patients undergoing percutaneous coronary intervention: the Sant'ANna TIrifiban Safety study, J. Cardiovasc. Med. 11 (2010) 250–259.
[24] M. Schiariti, A. Saladini, D. Cuturello, B. Missiroli, P.E. Puddu, Long-term efficacy of high-dose tirofiban versus double-bolus eptifibatide in patients undergoing percutaneous coronary intervention, J. Cardiovasc. Med. 12 (2011) 29–36.
[25] M. Schiariti, P. Saladini, D. Cuturello, L. Iannetta, C. Torromeo, P.E. Puddu, Decline in platelet count and long-term post-PCI ischemic events: implication of the intra-aortic balloon pump, Vasc. Pharmacol. 60 (2014) 25–31.
[26] S.A. Shah, R.J. Shapiro, R. Mehta, J.A. Snyder, Impact of enhanced external counterpulsation on Canadian Cardiovascular Society angina class in patients with chronic stable angina: a meta-analysis, Pharmacotherapy 30 (2010) 639–645.
[27] R.S. Taylor, J. De Vries, E. Buchser, M.J. Dejongste, Spinal cord stimulation in the treatment of refractory angina: systematic review and meta-analysis of randomised controlled trials, BMC Cardiovasc. Disord. 9 (2009) 13.
[28] J.R. McMullen, M.C. Sherwood, O. Tarnavski, et al., Inhibition of mTOR signaling with rapamycin regresses established cardiac hypertrophy induced by pressure overload, Circulation 109 (2004) 3050–3055.
[29] X.M. Gao, G. Wong, B. Wang, et al., Inhibition of mTOR reduces chronic pressure-overload cardiac hypertrophy and fibrosis, J. Hypertens. 24 (2006) 1663–1670.
[30] A.M. Siedlecki, X. Jin, A.J. Muslin, Uremic cardiac hypertrophy is reversed by rapamycin but not by lowering of blood pressure, Kidney Int. 75 (2009) 800–808.
[31] E. Paoletti, M. Amidone, P. Cassottana, M. Gherzi, L. Marsano, G. Cannella, Effect of sirolimus on left ventricular hypertrophy in kidney transplant recipients: a 1-year nonrandomized controlled trial, Am. J. Kidney Dis. 52 (2008) 324–330.
[32] S.S. Kushwaha, E. Raichlin, Y. Sheinin, W.K. Kremers, K. Chandrasekaran, G.J. Brunn, J.L. Platt, Sirolimus affects cardiomyocytes to reduce left ventricular mass in heart transplant recipients, Eur. Heart J. 29 (2008) 2742–2750.
[33] C. Castro, J.M. Campistol, D. Sancho, F. Sanchez-Madrid, E. Casals, V. Andrés, Rapamycin attenuates atherosclerosis induced by dietary cholesterol in apolipoprotein-deficient mice through a p27Kip1-independent pathway, Atherosclerosis 172 (2004) 31–38.
[34] M.M. Elloso, N. Azrolan, S.N. Sehgal, et al., Protective effect of the immunosuppressant sirolimus against aortic atherosclerosis in apo E-deficient mice, Am. J. Transplant. 3 (2003) 562–569.
[35] Z. Varghese, R. Fernando, J.F. Moorhead, S.H. Powis, X.Z. Ruan, Effects of sirolimus on mesangial cell cholesterol homeostasis: a novel mechanism for its action against lipid-mediated injury in renal allografts, Am. J. Physiol. Ren. Physiol. 289 (2005) F43–F48.
[36] M.A. Mueller, F. Beutner, D. Teupser, U. Ceglarek, J. Thiery, Prevention of atherosclerosis by the mTOR inhibitor everolimus in LDLR −/− mice despite severe hypercholesterolemia, Atherosclerosis 198 (2008) 39–48.
[37] S. Farsetti, M. Zanazzi, L. Caroti, et al., Lower homocysteine levels in renal transplant recipients treated with everolimus: a possible link with a decreased cardiovascular risk? Transplant. Proc. 42 (2010) 1381–1382.
[38] S. Schreml, K. Lehle, D.E. Birnbaum, J.G. Preuner, mTOR-inhibitors simultaneously inhibit proliferation and basal IL-6 synthesis of human coronary artery endothelial cells, Int. Immunopharmacol. 7 (2007) 781–790.
[39] S. Eckl, C. Heim, S. Abele-Ohl, J. Hoffmann, M. Ramsperger-Gleixner, M. Weyand, S.M. Ensminger, Combination of clopidogrel and everolimus dramatically reduced the development of transplant arteriosclerosis in murine aortic allografts, Transpl. Int. 23 (2010) 959–966.
[40] P.S. Brara, M. Moussavian, M.A. Grise, J.P. Reilly, M. Fernandez, R.A. Schatz, S. Teirstein, Pilot trial of oral rapamycin for recalcitrant restenosis, Circulation 107 (2003) 1722–1724 (Erratum in: Circulation 2003;108:2170).
[41] R. Waksman, A.E. Ajani, A.D. Pichard, et al., Oral rapamycin to inhibit restenosis after stenting of de novo coronary lesions: the oral rapamune to inhibit restenosis (ORBIT) study, J. Am. Coll. Cardiol. 44 (2004) 1386–1392.
[42] A.E. Rodríguez, M. Rodríguez Alemparte, C.F. Vigo, C. Fernández Pereira, C. Llauradó, D. Vetcher, A. Pocovi, J. Ambrose, Role of oral rapamycin to prevent restenosis in patients with de novo lesions undergoing coronary stenting: results of the Argentina single centre study (ORAR trial), Heart 91 (2005) 1433–1437.
[43] A.E. Rodriguez, M.R. Alemparte, C.F. Vigo, C.F. Pereira, C. Llaurado, M. Russo, R. Virmani, J.A. Ambrose, Pilot study of oral rapamycin to prevent restenosis in patients undergoing coronary stent therapy: Argentina single-center study (ORAR trial), J. Invasive Cardiol. 15 (2003) 581–584.
[44] F.S. Brito Jr., W.C. Rosa, J.A. Arruda, H. Tedesco, J.O. Pestana, V.C. Lima, Efficacy and safety of oral sirolimus to inhibit in-stent intimal hyperplasia, Catheter. Cardiovasc. Interv. 64 (2005) 413–418.
[45] J. Hausleiter, A. Kastrati, J. Mehilli, et al., Randomized, double-blind, placebo-controlled trial of oral sirolimus for restenosis prevention in patients with in-stent restenosis: the oral sirolimus to inhibit recurrent in-stent stenosis (OSIRIS) trial, Circulation 110 (2004) 790–795.
[46] A.E. Rodriguez, J.F. Granada, M. Rodriguez-Alemparte, et al., Oral rapamycin after coronary bare-metal stent implantation to prevent restenosis: the prospective, randomized oral rapamycin in Argentina (ORAR II) study, J. Am. Coll. Cardiol. 47 (2006) 1522–1529.
[47] A.E. Rodriguez, A. Maree, S. Tarragona, et al., Percutaneous coronary intervention with oral sirolimus and bare metal stents has comparable safety and efficacy to treatment with drug eluting stents, but with significant cost saving: long-term follow-up results from the randomised, controlled ORAR III (oral rapamycin in Argentina) study, EuroIntervention 5 (2009) 255–264.
[48] S. Kufner, J. Hausleiter, G. Ndrepepa, et al., Long-term risk of adverse outcomes and new malignancies in patients treated with oral sirolimus for prevention of restenosis, JACC Cardiovasc. Interv. 2 (2009) 1142–1148.
[49] A. Keogh, M. Richardson, P. Ruygrok, et al., Sirolimus in de novo heart transplant recipients reduces acute rejection and prevents coronary artery disease at 2 years: a randomized clinical trial, Circulation 110 (2004) 2694–2700.

Please cite this article as: A. Mischie, et al., Oral sirolimus: A possible treatment for refractory angina pectoris in the elderly, Int J Cardiol (2016), http://dx.doi.org/10.1016/j.ijcard.2016.07.206

[50] E. Paoletti, G. Cannella, Regression of left ventricular hypertrophy in kidney transplant recipients: the potential role for inhibition of mammalian target of rapamycin, Transplant Proc. 42 (2010) S41–S43, http://dx.doi.org/10.1016/j.transproceed.2010.07.007.
[51] M.R. Costanzo, A. Dipchand, R. Starling, et al., The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients, J. Heart Lung Transplant. 29 (2010) 914–956.
[52] C.G. Groth, L. Backman, J.M. Morales, et al., Sirolimus (rapamycin)-based therapy in human renal transplantation: similar efficacy and different toxicity compared with cyclosporine. Sirolimus European renal transplantation study group, Transplantation 67 (1999) 1036–1042.
[53] Y. Bottiger, J. Sawe, C. Brattstrom, et al., Pharmacokinetic interaction between single oral dose of diltiazem and sirolimus in healthy volunteers, Clin. Pharmacol. Ther. 69 (2001) 32–40.
[54] V. Vaccarino, L. Badimon, R. Corti, C. de Wit, M. Dorobantu, O. Manfrini, A. Koller, A. Pries, E. Cenko, R. Bugiardini, Presentation, management, and outcomes of ischaemic heart disease in women, Nat. Rev. Cardiol. 10 (2013) 508–518.
[55] L.G. Shewan, A.J. Coats, Adherence to ethical standards in publishing scientific articles: a statement from the International Journal of Cardiology, Int. J. Cardiol. 161 (2012) 124–125.
[56] F. Alfonso, A. Timmis, F.J. Pinto, et al., Conflict of interest policies and disclosure requirements among European Society of Cardiology National Cardiovascular journals, Eur. Heart J. 33 (2012) 587–594.
[57] ESC Board, Relations between professional medical associations and the health-care industry, concerning scientific communication and continuing medical education: a policy statement from the European Society of Cardiology, Eur. Heart J. 33 (2012) 666–674.

Please cite this article as: A. Mischie, et al., Oral sirolimus: A possible treatment for refractory angina pectoris in the elderly, Int J Cardiol (2016), http://dx.doi.org/10.1016/j.ijcard.2016.07.206