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

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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 therapeutic 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.

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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 over, most of the interventions for the treatment of RAP have a limited/slightly superior result for symptom’s regression and no effect.
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], 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 an 8.7% death rate at 4.2 years, which is consistent with some reports [6,7] and a 4.6% death rate/year at 2 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 (5.5% 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

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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-myocardic 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 proatherogenic 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-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),
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 2
Oral sirolimus and stents in randomized controlled clinical trials.

<table>
<thead>
<tr>
<th>Author/Method</th>
<th>Year of publication</th>
<th>Groups</th>
<th>No. of patients</th>
<th>Loading dose/daily dose</th>
<th>End-point Median FU period</th>
<th>TVR %</th>
<th>TLR %</th>
<th>Death/cardiac death %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodriguez et al. [47]</td>
<td>2009 De novo stenosis</td>
<td>OS plus BMS 100</td>
<td>10 mg one day before then 3 mg/day plus diltiazem SR 180 mg/day for 14 days</td>
<td>18.3 +/- 7 months</td>
<td>10.6</td>
<td>7.0</td>
<td>3.0/1.0</td>
<td></td>
</tr>
<tr>
<td>Rodriguez et al. [46]</td>
<td>2006 De novo stenosis</td>
<td>OS plus BMS 50</td>
<td>6 mg at 2.7 h before stent then 3 mg/day plus diltiazem SR 180 mg/day for 14 days</td>
<td>Restenosis and LLL @ 9 months. TVR, TLR and MACE @ 1 year</td>
<td>8.3</td>
<td>7.6</td>
<td>4.0/1.0</td>
<td></td>
</tr>
<tr>
<td>Rodriguez et al. [47]</td>
<td>2009 De novo stenosis</td>
<td>DES 100</td>
<td>No OS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rodriguez et al. [46]</td>
<td>2006 De novo stenosis</td>
<td>BMS 50</td>
<td>No OS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

Table 3
Adverse effects of oral sirolimus and stents.

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of patients on OS</th>
<th>Loading dose/daily dose</th>
<th>Timing of exams during follow-up</th>
<th>Discontinued medication</th>
<th>AE (%)</th>
<th>Sirolimus blood levels (ng/ml)</th>
<th>Gum sores</th>
<th>Diarrhoea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodriguez et al. [47]</td>
<td>100</td>
<td>10 mg one day before then 3 mg/day plus diltiazem SR 180 mg/day for 14 days</td>
<td>Baseline, 7 and 30 days plus regular interviews</td>
<td>4%</td>
<td>24%</td>
<td>NA</td>
<td>14%</td>
<td>12%</td>
</tr>
<tr>
<td>Rodriguez et al. [46]</td>
<td>50</td>
<td>6 mg at 2.7 h before stent then 3 mg/day plus diltiazem SR 180 mg/day for 14 days</td>
<td>Baseline, 7, 14 and 21 days plus regular interviews</td>
<td>4%</td>
<td>26%</td>
<td>11.46 +/- 4.5 at baseline</td>
<td>16%</td>
<td>6%</td>
</tr>
<tr>
<td>Waksman et al. [41]</td>
<td>30</td>
<td>5 mg immediately before or after BMS then 2 mg/day for 30 days</td>
<td>Baseline, 30 days and 6 months.</td>
<td>10%</td>
<td>43.3%</td>
<td>5.3 +/- 3.1 at day one, 6.4 +/- 4.2 at 30 days</td>
<td>13.3%</td>
<td>16.6%</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>5 mg immediately before or after BMS then 5 mg/day for 30 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hausleiter et al. [45]</td>
<td>99</td>
<td>6 mg 1 day before BMS then 2 mg/d for 8 days</td>
<td>Day of procedure, third day after procedure and at 6 months.</td>
<td>3%</td>
<td>3%</td>
<td>10.0 +/- 8.5 day of the procedure, 6.6 +/- 4.9 at day 3 afterwards</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>99</td>
<td>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</td>
<td></td>
<td>4%</td>
<td>4%</td>
<td>18.1 +/- 5.2 day of the procedure, 10.5 +/- 5.0 at day 3 afterwards</td>
<td>NA</td>
<td>1</td>
</tr>
<tr>
<td>Brara et al. [40]</td>
<td>22</td>
<td>6 mg after PTCA then 2 mg/d for 30 days</td>
<td>Baseline, 1, 3 and 5 w after intervention</td>
<td>50% (treatment duration of 14.5 +/- 6.5 days)</td>
<td>50%</td>
<td>3.9%</td>
<td>25%</td>
<td>5.2</td>
</tr>
<tr>
<td>Rodriguez et al. [42,43]</td>
<td>76</td>
<td>6 mg after BMS then 2 mg/d (plus or minus diltiazem 180 mg/day) for 30 days</td>
<td>Baseline, 1, 3 and 4 w after intervention</td>
<td>3.9%</td>
<td>25%</td>
<td>Ø 3 weeks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: OS-oral sirolimus; SR-slow release; BMS-bare metal stents; PTCA-percutaneous transluminal coronary angioplasty; AE-adverse effects; NA-non-available.
### Table 2

<table>
<thead>
<tr>
<th>In-stent restenosis (%)</th>
<th>MACE %</th>
<th>Discontinued medication %</th>
<th>Diabetes mellitus %</th>
<th>LVEF Reference diameter/lesion length</th>
<th>No. of lesions</th>
<th>Type of lesion</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.2%/NA</td>
<td>9%</td>
<td>(TVR and TLR not included)</td>
<td>4</td>
<td>&lt;40% in 11%</td>
<td>158</td>
<td>A + B1: 38.8%</td>
<td>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.</td>
</tr>
<tr>
<td>6.4%/NA</td>
<td>15%</td>
<td>(TVR and TLR not included)</td>
<td>NA</td>
<td>&lt;40% in 6%</td>
<td>170</td>
<td>B2 + C: 67.8%</td>
<td></td>
</tr>
<tr>
<td>11.6%/0.73 +/-0.40</td>
<td>20%</td>
<td>(TVR included)</td>
<td>4</td>
<td>2.96 +/-0.64/13.35 +/-6.33</td>
<td>66</td>
<td>B2: 46.5%</td>
<td>OS significantly reduces angiographical and clinical parameters of restenosis.</td>
</tr>
<tr>
<td>36.4%/1.41 +/-0.67</td>
<td>44%</td>
<td>(TVR - included)</td>
<td>NA</td>
<td>2.91 +/-0.41/12.79 +/-4.28</td>
<td>59</td>
<td>C: 22.7%</td>
<td></td>
</tr>
<tr>
<td>42.2%/0.60 +/-0.56</td>
<td>2%</td>
<td>(30 days) 27.5% (1 year, including TVR)</td>
<td>0</td>
<td>27.5</td>
<td>NA</td>
<td>B1: 8%</td>
<td>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.</td>
</tr>
<tr>
<td>38.6%/0.72 +/-0.70</td>
<td>3%</td>
<td>(30 days) 29.3% (1 year, including TVR)</td>
<td>3</td>
<td>27.3</td>
<td>NA</td>
<td>B2: 39%</td>
<td></td>
</tr>
<tr>
<td>22.1%/0.49 +/-0.54</td>
<td>2%</td>
<td>(30 days) 18.2% at 1 year (including TVR)</td>
<td>4</td>
<td>32.2</td>
<td>NA</td>
<td>B3: 20.3%</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3

<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>Constipation</th>
<th>Gastritis</th>
<th>Rash</th>
<th>Fever</th>
<th>Psoriasis</th>
<th>Angioedema</th>
<th>Nausea and vomiting</th>
<th>Triglyceride increase but normalized at FU</th>
<th>Leucopenia % (normalized at follow-up)</th>
<th>Mild hepatic dysfunction (normalized at follow-up)</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>NA</td>
<td>NA</td>
<td>Decrease by 5.4%</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0%</td>
<td>1%</td>
<td>3%</td>
<td>5%</td>
<td>1%</td>
<td>1%</td>
<td>NA</td>
<td>NA</td>
<td>Increase by 23%</td>
<td>Decrease by 32.5%</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>NA</td>
<td>6.6%</td>
<td>NA</td>
<td>NA</td>
<td>6.6%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>NA</td>
<td>36.6%</td>
<td>NA</td>
<td>NA</td>
<td>3.3%</td>
<td>Severe increase in3.3%</td>
<td>Severe decrease in 6.6% patients</td>
<td>3.3%</td>
<td>3.3% (fatigue)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1%</td>
<td>NA</td>
<td>Decreased by 8.6%</td>
<td>NA</td>
<td>1% (infections)</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>2 (suspected allergy)</td>
<td>NA</td>
<td>NA</td>
<td>Decreased by 22%</td>
<td>NA</td>
<td>1% (infections)</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>13.6%</td>
<td>13.6%</td>
<td>4.5%</td>
<td>4.5%</td>
<td>4.5% (acnea)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.6</td>
<td>1.3</td>
<td>9.2</td>
<td>2.6</td>
<td>NA</td>
<td>1.3</td>
<td>NA</td>
<td>Negative</td>
<td>NA</td>
<td>1.3% (headache), 1.3% (insomnia)</td>
<td></td>
</tr>
</tbody>
</table>

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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 ORASY 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 OSIROS 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).
Acknowledgement and conflict of interest

The authors do not report relationships that could be construed as a conflict of interest [55–57].

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