The Ravel Trial. Zero Percent Restenosis: A Cardiologist's Dream Comes True!

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Since the introduction of coronary angioplasty, every advance has been shadowed by the phenomenon known as «restenosis». Attempts to avoid the vascular reaction naturally generated by «mother nature» in response to the vascular damage induced by catheterization have either failed or had only limited success. Nevertheless, the findings of the recently published RAVEL study seem to indicate that the dream of generations of cardiologists seems to have come true and restenosis has been relegated to the kingdom of nightmares and fairy tales.

Such «sweet dreams» are made of «rapamycin»

Rapamycin (sirolimus) is a drug that has been approved by the FDA (Food and Drug Administration) for the prophylaxis of rejection in renal transplantation (Rapamune®) since 1999. It is a natural macrocyclic lactone that blocks the passage from G1 to S in the cell cycle, and interacts with a specific target protein (mTOR [mammalian Target Of Rapamycin]) to inhibit its activation. Inhibition by mTOR (FK506-binding protein 12) suppresses T-cell proliferation induced by cytokines (IL-2, IL-4, IL-7 and IL-15). The mTOR protein is a key kinase regulator and its inhibition produces several important effects, including: *a)* inhibition of the translation of a messenger RNA family that encodes proteins essential to the progression of the cell cycle; *b)* IL-2 induced inhibition of the transcription of proliferating cell nuclear antigen (PCNA), which is essential for DNA replication; *c)* blockade of CD28-mediated up-regulation of IL-2 transcription in T cells, and *d)* inhibition of the kinase activity of cdk4/cyclin D and cdk2/cyclin E complexes, essential for progression of the cell cycle. Its mechanism of action is different from that of other immunosuppressive agents that only act to inhibit DNA synthesis, such as mycophenolate mofetil (CellCept®) and azathioprine (Imuran®). Rapamycin has a synergic action with cyclosporin A and much less toxicity than other immunosuppressive drugs.

The sirolimus-coated stent «BX velocity» (Cypher) is manufactured from medical stainless steel (316 LS) and measures 18 mm in length. This stent contains 140 mg/cm^2 of rapamycin, for a total rapamycin content of 153 mg in the 6-cell stent and 180 mg in the 7-cell stent. The formulation of the coating consists of 30% rapamycin by weight in a 50% polymer mixture: polyethylene vinyl acetate (PEVA) and polybutylmethacrylate acetate (PBMA).

History of this development

The first experimental studies demonstrated that rapamycin impeded the proliferation of T cells and the proliferation[1] and migration of smooth muscle cells.[2-5] Studies of its effectiveness in rabbit and pig models also demonstrated a reduction of intra-stent intimal hyperplasia by 35% to 50% at 28 days in stents coated with rapamycin compared bare metal stents.[6]

The São-Paulo Registry

Thirty patients with angina pectoris were treated with electively with two different formulations of the BX Velocity® stent (Cordis) with rapamycin (15 patients with a slow-release [SR] formulation and 15 with a fast-release [FR] formulation). All stents were implanted successfully and patients were released without clinical complications. In the angiographic follow-up and intravascular echography (IVUS) at 4

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months, minimal neointimal hyperplasia was appreciated in the 2 groups (amount of neointima per IVUS 11.0%±3.0% [SR] and 10.4%±3.0% [FR]; delayed intra-stent loss by quantitative angiography 0.09±0.3 mm [SR] and 0.02±0.3 mm [FR]).[7] At one year of follow-up, volumetric analysis by IVUS as well as angiography again demonstrated a minimal amount of neointimal hyperplasia, similar to that observed at 4 months, in both groups. In addition, some patients showed no evidence of neointimal hyperplasia. In the FR group, a late myocardial infarction took place (at 14 months), but no other major cardiac events were detected and no patient in either group developed restenosis.[8]

The Rotterdam Registry

In Rotterdam, 15 patients were treated. All stents were implanted successfully. One patient died after 2 days due to cerebral hemorrhage and another one suffered subacute occlusion of the stent due to residual dissection. In the quantitative angiography made at 6 months, no changes were appreciated in the minimal luminal diameter or percentage of stenosis. Therefore, no instances of restenosis occurred within the stent or in any part of the segment treated. No instances of «edge effect» proximal or distal to the stent were seen. In the follow-up at 9 months, no additional adverse events were recorded and all patients remained free of angina.[9]

RAVEL Study (Randomized study with sirolimus-coated BX Velocity balloon-expandable stent in the treatment of patients with de novo native coronary artery lesions)

A total of 238 patients with lesions *de novo* were randomized to receive a single stent, either a sirolimus-coated stent or a conventional BX Velocity stent. In the follow-up at 6 months, the group treated with rapamycin-eluting stents showed no restenosis, no late loss of luminal diameter, and no reinterventions of the responsible vessel![10,11]

These clinical results are absolutely spectacular because they convincingly demonstrate, in all patients, the absence of neointimal proliferation in the first 6 months after stent implantation, a phenomenon that has never before been seen.

Too good to be true?

The first presentation of this study at the AHA meeting in 2001 in Anaheim caused an interesting reaction: the cardiological community promptly divided into «believers» and «nonbelievers». In the light of these unambiguous results, scientists, investigators, and cardiologists, all of them with strong roots in the tradition of objectivity and evidence-based decision-making, suddenly formed «emotional» opinions. How we can explain such a paradox?

Could it be the study design?

No, the study was designed as a prospective, multicenter, random, double-blind trial. The data were analyzed by an external laboratory, which did not know what treatment was received, using standardized and well validated analysis algorithms.

Could it have been the endpoint analyzed?

The main objective of the study was late angiographic loss of vessel diameter. This translates into a mechanistic approach to the study of the effect of the drug. It could be argued that this technical parameter has only secondary clinical importance. Nevertheless, this variable is closely related to the clinical need for revascularization of the target lesion. Even so, the superiority of stents coated with sirolimus was not limited the main study endpoint, but persisted when analyzing the clinical episodes responsible for major adverse cardiac events during follow-up.

Could it have been patient selection?

Clearly, the inclusion criteria restricted the study group to a low-risk population (for the procedure and restenosis) of patients with short, *de novo* lesions of native coronary arteries. Patients with a high risk of restenosis were excluded, such as those that present severe kidney failure, long lesions, or lesions of bifurcations, ostia, or multiple lesions. Nonetheless, in the past similar inclusion criteria have not affected the credibility of studies that are important for interventionist cardiology, like the STRESS and BENESTENT studies.

Could it be the interpretation of the results?

This raises the question of if whether the outcome of the treated group was too good or, on the contrary, the outcome of the control group was too unfavorable. Nevertheless, the rate of restenosis of 26% found in the control group was very realistic considering that approximately 40% of the vessels included in the RAVEL study were of small caliber (<2.5 mm). Possible doubts about the comparative value of the group control should not distract our attention from the excellent results obtained in the patients of the treated group. This is important, because this information seems to be extremely solid and unaffected by the classic coronary risk factors like sex, diabetes, vessel size, or site of the lesion. Other studies that in the past managed to demonstrate a strikingly

low rate of restenosis were the MUSIC study (8.3%)[12] and WEST II study (12%).[13] Nonetheless, it should be remembered that these studies were multicenter registries of stents in which implantation was optimized using intravascular echography. Similar results could not have been reproduced in randomized studies.[14] Once again, this only highlights the exceptional behavior of the treated group in the RAVEL trial.

Are we afraid of our own success?

Our efforts aimed at preventing restenosis have generated a formidable armamentarium of highly sophisticated instruments and well-trained interventionist cardiologists who can manage any lesion. If the promise of the RAVEL study, which is basically to eradicate restenosis, holds true, we will be witnessing a new era in interventionist cardiology, cardiac surgery, and health economics. These potentially enormous implications may very well be the key to the «emotional» judgments and assessments that we are currently observing.

Will we suffer a rude awakening?

In truth, there are still many unanswered questions. In the first place, we need long-term studies to determine if the drug inhibits neointimal growth permanently or simply delays it. At the moment, the clinical results favor sirolimus. The clinical course of patients remains stable and the rate of events is very low after one year of follow-up in the RAVEL study, 18 months in the Rotterdam series, and 2 years of follow-up of the pilot Sãao Paulo registry. Secondly, recent experience with brachytherapy has taught us to look for «unexpected phenomena», like positive remodeling, late stent repositioning, the edge effect, or delayed thrombosis. Until now, IVUS data seem to suggest the presence of a degree of positive remodeling and late stent repositioning that, nevertheless, does not seem to be clinically relevant since the clinical outcome of these patients is very good. Once again, it is essential to carry out a meticulous clinical, angiographic, and IVUS follow-up of these patients in the future. The third reason for concern is the generalization of the results of RAVEL study. Does the sirolimus-coated stent work in all types of patients and lesions? Recent experimental studies suggest that sirolimus could also be useful in the prevention of intra-stent restenosis. The antiproliferative effects of sirolimus after coronary interventions have been attributed to the inhibition of pRB phosphorylation, which impeded the down-regulation of $p27^{kip1}$.[15] This hypothesis is supported by findings in human carotid arteries.[16] Intense up-regulation of FK506-binding protein 12 has been detected in the neointimal tissue of lesions that suffer restenosis, whereas this protein was not detected in the smooth muscle cells of the medial layer that were used as controls. The effectiveness of sirolimus in restenotic lesions, intra-stent restenosis, long or branched lesions, total occlusions, or saphenous grafts must still be investigated.

The excellent result of the RAVEL multicenter, randomized study should not be interpreted as a simple «extrasystole» in more than 20 years of investigation of the phenomenon of restenosis. The study is in full agreement with the first pilot studies in humans and has confirmed their results. Zero percent restenosis will remain a milestone in the history of percutaneous coronary interventionist medicine and will constitute the gold standard against which any alternative treatment modality will be measured.

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