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Sirolimus treatment of left ventricular hypertrophy: who, and when?

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This editorial refers to 'Sirolimus affects cardiomyocytes to reduce left ventricular mass in heart transplant recipients'† by S.S. Kushwaha et al., on page 2742

The protein known as mammalian target of rapamycin (mTOR) plays vital roles in protein synthesis, and hence in growth and cell proliferation, including the proliferation of immune response cells and neoplastic cells. The paths through which it acts have two main branches that start from mTOR complexes known as mTORC1/RAPTOR and mTORC2/RICTOR. The former is inhibited by sirolimus (rapamycin), everolimus, and their analogues, while the latter is not. Despite not inhibiting mTORC2/RICTOR, the sirolimus family are known collectively as mTOR inhibitors, and also as proliferation signal inhibitors (PSIs).[1]

mTOR inhibitors are attractive for post-transplantation therapy because their antiproliferative properties appear to combine immunosuppression with reductions in the risk or progression of proliferative post-transplantation complications, notably malignancy[2] and allograft vasculopathy.[3,4] When replacing antimetabolites in triple therapy in conjunction with calcineurin inhibitors (CNIs) and steroids, mTOR inhibitors have been reported to decrease the progression of cardiac allograft vasculopathy without increasing the incidence of acute rejection;[4–6] and as replacements or partial replacements of CNIs they have been found both to attenuate the progression of allograft vasculopathy after heart transplantation (HT)[7] and to reduce the incidence of malignancy after kidney transplantation.[8]

Kushwaha *et al.*[9] have presented results suggesting that mTOR inhibitors may actually bring about the reversion of another common life-threatening post-HT complication, left ventricular hypertrophy (LVH).[10] In a retrospective study in which 83 patients with a CNI as primary immunosuppressor were compared over 1 year with 58 for whom a CNI was replaced with sirolimus because of nephrotoxicity and/or allograft vasculopathy, the authors found that LV mass index (LVMI) decreased significantly from 99 to 93 g/m^2 in the sirolimus group while increasing slightly in the CNI group, and that left atrial volume index, an indirect measure of diastolic function, decreased significantly in the sirolimus group while increasing significantly in the CNI group. Moreover, the reduction in LVMI was almost entirely found in the 13 sirolimus-treated patients with LVH at baseline, among whom average LVMI fell by 24 g/m^2. These results are in keeping with reports that in mice sirolimus reduces overload-induced LVH and fibrosis, and reverses associated alterations of gene expression;[11,12] and that in kidney transplant patients

with allograft nephropathy, replacement of CNIs with sirolimus may bring about the regression of LVH independently of blood pressure changes.[13]

Kushwaha *et al.* tentatively attribute the observed regression of LVH to the direct action of sirolimus on myocardium rather than to any influence on hypertension, the main cause of LVH in HT patients.[14] They base this conclusion on the fact that although blood pressure fell in the sirolimus group and not in the CNI group (doubtless because of the withdrawal of CNIs in the former), the blood pressure changes in the sirolimus group were not correlated with LVMI; and on the observation that the number of endomyocardial biopsy cells stained by a polyclonal antibody against the cell cycle inhibitor p27Kip1 increased in a group of 22 sirolimus-treated patients but not in a group of nine CNI-treated patients. In this respect, one misses the presentation of data on whether the p27Kip1-positive cell count correlated with the degree of LVH regression. Also, although increased p27Kip1 synthesis is not entirely unexpected (being a known effect of mTOR inhibition),[15] it is a pity that the results of labelling with polyclonal antibody were not backed up by reverse transcription–PCR or expression array studies. Such studies might have confirmed alteration of the complex pathway between mTOR and p27Kip1, and thrown light on whether alteration of other signalling pathways might also have been involved in the observed regression of LVH. Given the central physiological roles of mTOR, it is certainly on the cards that its inhibition has as yet unknown consequences,[16] and that any such consequences may include effects that are relevant to LVH.

Even if sirolimus does induce LVH regression in addition to its antitumoural, antivasculopathic, and immunosuppressive effects, it is not a panacea. As might be expected, given the very fundamental functions of mTOR, the administration of mTOR inhibitors has been associated with numerous adverse side effects with varying degrees of manageability, including hyperlipidaemia, defective wound healing, oedema, bacterial infections, acne, pneumonitis, and proteinuria.[17] Together with the immunosuppressive action of mTOR inhibitors, these effects call for great caution to be exercised in regard to the tacit suggestion of Kushwaha *et al.* that sirolimus may be a valid therapeutic approach to LVH in non-transplant patients.

The renal effects of replacing CNIs with mTOR inhibitors are particularly controversial. Although mTOR inhibitors are not themselves nephrotoxic, and their substitution for CNIs therefore reduces renal insult, there have been reports that total withdrawal of CNIs increases the risk of kidney graft rejection,[18] while partial withdrawal is called into question by reports that mTOR inhibitors potentiate the nephrotoxicity of CNIs.[17] Other studies have observed improved renal function without increased rejection risk in the total absence of CNIs,[3,19] or that renal function improved when low-level CNI administration accompanied administration of an mTOR inhibitor. Since the increased rejection risk seems mainly to affect patients in their first post-transplant year, some authors have recommended that mTOR inhibitors be used in conjunction with low-level CNI administration during this period.[17]

Another factor to be taken into account is the possible desirability of administering mTOR inhibitors together with additional drugs that counteract some of the mechanisms by which the cell responds to mTOR inhibition. It is known that there is a negative feedback loop whereby inhibition of mTORC1 by sirolimus increases AKT activation, which tends to restore mTOR activity;[20] and Carracedo *et al.*[21] have recently reported that cancer patients exhibit a second negative feedback loop, with similar effects, involving the mitogen-activated protein kinase pathway.

Kushwaha *et al.*'s findings open up exciting perspectives for the treatment of post-HT LVH. They call for more thorough evaluation in randomized trials that allow overall assessment of the pros and cons of mTOR inhibitor therapy. mTOR inhibitors certainly seem to have a role to play in the management of transplant patients; in the coming years, further research must characterize that role more fully.

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