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Focus

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Further evidence for the potential role of mTOR inhibitors in the prevention of post-transplantation hepatic fibrosis

The calcineurin inhibitors (CNIs) cyclosporine A and tacrolimus have been the cornerstone of anti-rejection drugs in liver transplantation for the last two decades. Recently, a new generation of anti-rejection agents is attracting the attention of transplant surgeons and hepatologists. Although not yet approved for routine use in liver transplantation, the mTOR inhibitors sirolimus and everolimus have been shown to be potent anti-rejection drugs that are less nephrotoxic when compared to CNIs and in addition seem to increase post-liver transplantation survival of patients with hepatocellular carcinoma [1,2]. Recent observations in experimental models of hepatic fibrosis in rats suggest that the sirolimus mTOR inhibitor Rapamycin also possesses superior anti-fibrotic properties [3,4]. This property may be of particular importance in patients undergoing liver transplantation for hepatitis C virus (HCV) infection. Such patients become uniformly re-infected with HCV post-transplantation and up to one third develop an accelerated course of hepatic fibrosis within five years. Yet, the cumulative experience using mTOR inhibitors after liver transplantation is rather limited. The potential anti-fibrotic activity of sirolimus is of particular interest especially in view of the recent conclusion supported by a metanalysis which did not confirm initial expectations of a superior anti-fibrotic effect of cyclosporine A over tacrolimus in post-transplant HCV patients [5]. Experimental evidence has already been presented stating that sirolimus-based immune suppression may prevent angiogenesis, limit tumor growth and induce microthrombi in liver tumors. It now becomes important to verify whether the anti-fibrotic properties of mTOR inhibitors will justify a broader use of these compounds in post-transplant HCV patients who are prone to develop an accelerated course of hepatic fibrosis.

In the present issue of the Journal, Patsenker and co-workers have used an experimental bile duct ligation (BDL) model in rats to compare the anti-fibrotic activity of four immuno-suppressive anti-rejection agents: cyclosporine A, tacrolimus, sirolimus, and everolimus. In their meticulously performed experiments, the investigators have used a number of complementary methods to evaluate the anti-fibrotic activity of the tested agents. These include standard liver function tests, liver histology, immunohistochemistry of inflammatory markers and morphometry, hepatic hydroxy proline analysis, measurement of collagenase activity, measurement of *Fibulin-2* mRNA and a number of fibrosis related gene expression analyses, evaluation of portal pressure as well as analysis of hepatic free fatty acids and triglycerides. Control groups included sham operated and non-treated BDL rats. Drug levels of all four tested compounds injected i.p. were monitored periodically.

The main finding of this experimental work suggests that the mTOR inhibitors sirolimus and everolimus, but not calcineurin inhibitors, suppress the development of hepatic fibrosis by up to 70% in bile duct ligated rats and that this effect is associated with decreased portal pressure. Furthermore, treatment with mTOR inhibitors led to down-regulation of pro-fibrotic genes, increased matrix degradation, suppression of inflammatory markers and improved histo-pathologic features manifested by an increased number of hepatocytes and decreased proliferation of cholangiocytes and myofibroblast like cells.

The strength of this study is the head to head evaluation of the four tested compounds using an *in vivo* model under controlled experimental conditions. At present, experience with mTOR inhibitors in liver transplant patients is very limited and information on the relative anti-fibrotic potential of sirolimus and everolimus versus calcineurin inhibitors is still unavailable. This is of particular importance in view of conflicting observations reported *in vitro*, using cell culture assays of human or rat stellate cells as well as some contradictory clinical observations in transplanted patients treated with calcineurin inhibitors. It may take some time until such an in depth comparative study as presented by Pastenker *et al.* can be conducted in human patients. Thus, the results of these experiments, using an extensive number of complementary methods in one cohort of animals, contain a wealth of information which will be of particular interest to investigators and practitioners in the field. The authors of this study emphasize the potential implication of their results on the management and prevention of hepatic fibrosis in patients undergoing liver transplantation for chronic HCV infection. Yet, as also stated by the investigators themselves in their discussion, the study has a limitation due to the selected study model of bile duct ligation. The generation of hepatic fibrosis in the BDL model is a very rapid process, which occurs within 2–5 weeks of bile duct ligation as a result of mechanical obstruction of biliary drainage and cholagiole proliferation in a non-infected animal. In contrast, in humans, HCV infection leads to a necro-inflammatory process which is at least driven in part by an immunological mechanism leading to a gradual and much slower development of hepatic fibrosis. Furthermore, additional factors including viral replication, host and virus genetic properties and use of pharmacologic agents in the post-transplant setting may also have an impact on

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generation of hepatic fibrosis. Thus, the mechanism involved in the fast generation of hepatic fibrosis in the BDL model is most likely very different from the process which occurs in human post-transplantation HCV re-infection even if the post-transplantation fibrosis may evolve in some patients more rapidly compared to non-transplanted patients. Unfortunately, all of the available experimental models for HCV infection such as the transgenic mouse, the uPA/albumin humanized mouse, the trimera mouse or even the chimpanzee models have their own limitations especially when it concerns the development hepatic fibrosis. Therefore, despite its drawback, the BDL model provides an opportunity to study and compare the anti-fibrogenic activity of the tested anti-rejection agents in a controlled and systematic manner. Consequently, the encouraging results of this study confirming the superior anti-fibrogenic activity of sirolimus and everolimus justify further evaluation in controlled clinical trials in liver transplant patients infected with HCV.

Conflict of interest

The author declared that he does not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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