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Sirolimus – It doesn't deserve its bad Rap(a)

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There are few medications in the field of transplantation that evoke such strong opinions as Sirolimus – it is either loved or loathed. Initial concerns about side effects and the 2002 black box warning from the Food and Drug Administration (FDA) regarding the risk of hepatic artery thrombosis (HAT) meant that for many years, Sirolimus was not used widely in liver transplantation. However, recent data show that Sirolimus offers potential benefit in specific areas such as hepatocellular carcinoma (HCC) and hepatitis C virus (HCV)-infected grafts, with acceptable risk to benefit ratios. It's time to recognize that Sirolimus offers safe and effective immune suppression following liver transplantation.

Sirolimus was initially approved for renal transplantation by the FDA in 1999 and its' use in liver transplantation was met with high expectations. However based on the results of two multicenter trials (Wyeth 211 and 220) Sirolimus was not approved by the FDA for liver transplantation and instead, a black box warning was placed on its use. Specifically the warning stated Sirolimus "was associated with excess mortality and graft loss in a study in *de novo* transplant patient" and "associated with an increase in HAT; most cases of HAT occurred within 30 days post transplantation and most led to graft loss or death" [1]. Unfortunately neither study has been submitted for peer review, so the transplant community has been unable to review the data.

Contrary to general perception, these two trials contained conflicting data, especially regarding the incidence of HAT. In the first trial (Wyeth 211) a study of 111 patients taking Sirolimus and Ciclosporin was compared with 52 Tacrolimus 'controls'; there was no statistical difference in HAT (9.0% *vs.* 3.8%, $p = 0.10$), graft survival or patient survival and the incidence of rejection was lower with Sirolimus [2]. The second study (Wyeth 220), which compared 110 patients taking Sirolimus and Tacrolimus with 112 Tacrolimus 'controls' was halted prematurely.

There was no statistical difference in HAT (5.5% *vs.* 0.9%, $p = 0.07$) although there were higher rates of graft loss and death [3]. These trials formed the basis of the black box warning regarding HAT and survival, but neither trial showed that HAT occurred at a higher rate than expected, while one showed significantly worse graft and patient survival with Sirolimus.

Since 2000 there have been 20 published reports of *de novo* mTOR inhibitor use in liver transplantation and all have shown either a reduced incidence of HAT with Sirolimus, or no difference compared to controls [4–15]. Furthermore, all have shown either improved, or similar, patient and graft survival with Sirolimus. There have been no published reports to confirm the results leading to the black box warning. In contrast, a large report of the combined experience of 252 patients from the University of Colorado and University of Alberta described an HAT incidence of 1.2% in those receiving Sirolimus, which was significantly lower than in controls. The 1-year and 5-year patient survival of 92% and 84% were statistically similar to controls [8]. This paralleled our large experience from the Baylor Transplant Institute of 371 patients receiving *de novo* Sirolimus in liver transplantation, which showed a significantly lower incidence of HAT (1.1%) with Sirolimus compared to controls. We went more than 11 years and over 300 consecutive *de novo* Sirolimus-treated patients without seeing HAT on Sirolimus. Additionally we found similar 1-year and 5-year patient survival of 93% and 76% with Sirolimus [16]. While both studies are retrospective, when combined, the number of patients (more the 600) treated *de novo* with Sirolimus dwarves the 221 patients in the trials used by the FDA and both centers' nearly identical experience validate their accuracy and show that Sirolimus actually reduces the risk of HAT – the opposite of what has been shown before.

Despite the black box warning, many centers have relied on their long term experience with Sirolimus to assess its value. Many experienced clinicians recognize the potential benefit of off-label Sirolimus use, since 12% of liver recipients in the United States receive Sirolimus during the first year. As with other immunosuppressants, Sirolimus is associated with side effects; these include hyperlipidemia, mouth ulcers, poor wound healing, and hematological issues, but increased familiarity has made it easier to manage side effects.

Hyperlipidemia is the most common side effect from Sirolimus affecting up to 45% of liver recipients and often cited as a concern for patient safety [17]. The dyslipidemia can be controlled with omega-3 fatty acids from fish oil and statins [18]. Despite the dyslipidemia, Sirolimus has not been shown to have a negative impact on cardiovascular events; randomized studies show that Sirolimus does not represent a risk factor for cardiovascular disease [19]. The reverse may in fact be true, since several *in vivo* studies have demonstrated that Sirolimus reduces atherosclerotic lesion formation. This suggests that even if Sirolimus-induced dyslipidemia is atherogenic, it is countered by the anti-inflammatory and anti-proliferative effects of Sirolimus [20–21].

The other side effects of Sirolimus are also managed easily. Mouth ulcers were a common cause for discontinuation, but treatment with topical kenalog-in-orobase eliminates pain and heals the ulcer in 2–3 days without discontinuation. Poor wound

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healing is also a concern, based on the role of the mTOR pathway in fibrosis. Some centers accommodate this concern by delaying Sirolimus until 1–2 weeks after transplantation. We use Sirolimus immediately post-op and has not found a significant problem with wound healing, although in larger, diabetic patients, we use an incision-line wound vac on top of the staples, to remove fluid from the wound and pull the tissue together. If major surgery is needed, Sirolimus can be replaced temporarily with Mycophenolate for 3 weeks peri-operatively and patients converted back post-operatively without incident. Hematological issues such as thrombocytopenia and leukopenia have been reported, although the large studies of Sirolimus use in liver transplantation do not show any difference in the incidence of hematological side effects [8]. Our experience found leukopenia in 40% of patients, which was reversible over time. Despite the leukopenia, there was no difference in bacterial and fungal infection, while viral infections such as CMV were reduced significantly on Sirolimus [4,16]. Pneumonitis, which affects 1–2% of liver transplant patients and is characterized by diffuse bilateral pulmonary infiltrates without a clear infectious etiology, represents the one side effect that requires discontinuation of Sirolimus [22].

Recent studies have identified potential new benefits from using Sirolimus that alter the risk-benefit ratios. mTOR inhibitors are anti-neoplastic because of their anti-proliferative and anti-angiogenic properties and they are now approved as anti-tumor agents. For liver transplant recipients with hepatocellular carcinomas (HCC) three large studies have shown a significant beneficial impact of Sirolimus on 5-year survival [4–6]. Comparing Sirolimus with 'control' Chinnakotla *et al.* reported 5-year survival of 80% *vs.* 59%, Zimmerman *et al.* reported 80% *vs.* 62%, and Toso *et al.* reported 83% *vs.* 68.7%, respectively. Toso sums his study up succinctly, stating "twice as many recipients not on Sirolimus died from cancer".

Renal dysfunction from long-term use of calcineurin inhibitors (CNI) is a major concern and mTOR inhibitors avoid this morbidity. Early studies of the impact of Sirolimus on post-transplant renal function yielded mixed results because Sirolimus was not given *de novo* or prescribed after renal dysfunction was already established. The first prospective randomized trial of *de novo* mTOR inhibitor use in routine liver transplants showed improved GFR and a significantly lower incidence of advanced chronic kidney disease, demonstrating that mTOR inhibitors can limit renal dysfunction in liver transplantation [23].

More exciting benefits from Sirolimus are being elucidated and may change the field of transplant. Recent data from our center have shown that *de novo* Sirolimus reduces HCV related fibrosis progression markedly when evaluated by annual protocol biopsy and multivariate analysis showed Sirolimus to be the only independent predictor of low fibrosis stage post-transplant [24]. Since recurrent HCV is the major cause of allograft failure, this could have a major impact on long-term allograft survival. Another potential benefit from Sirolimus use is the impact of Sirolimus on weight gain in liver transplant recipients. Recent data demonstrate that Sirolimus prevents characteristic post-transplant weight gain, a major cause of morbidity [25].

Substantial evidence from many centers demonstrates that concerns about HAT with *de novo* Sirolimus use are unwarranted. Growing experience with Sirolimus has taught us how to manage side effects. In light of this and with many of the benefits from Sirolimus suggesting a major impact on long-term patient and graft survival for patients transplanted with HCC and HCV and the potential for Sirolimus to limit significant post-transplant co-morbidity such as weight gain and renal dysfunction, it is becoming difficult to argue against its use in well defined populations.

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