

**Report of the 13th Annual International Congress of the ILTS,
June 20-23, 2007, Rio de Janeiro, Brazil
for the Novartis Transplantation Advisory Board Grant**

Plenary Session II

Room Location: Gavea A&B, 8:00 – 10:00 am

Chairs: Jacques Belghiti, MD & Geoffrey McCaughan, MD

Introduction

During the ILTS 2007 meeting in Rio de Janeiro, Brazil, I presented my abstract “Is intraoperative aprotinin prophylaxis associated with the development of renal dysfunction or failure after liver transplantation? An analysis of 1067 patients.” in this plenary session. Perhaps because of the varied opinions about this very subject, it turned out to be a quite busy session with a lively discussion.

The intraoperative use of aprotinin during orthotopic liver transplantation (OLT)

Historically orthotopic liver transplantation has been associated with a high risk of massive intraoperative blood loss. However, during the last decade, blood loss and transfusion requirements have diminished substantially due to increasing experience, improvements in surgical and anesthesiological methods, and the use of antifibrinolytic drugs. The use of aprotinin in liver transplant recipients was first reported by Neuhaus et al. and Mallett et al. more than 15 years ago. In randomized controlled trials, prophylactic administration of aprotinin has been shown to reduce blood loss and transfusion requirements in patients undergoing liver transplantation by about 30%.

Two recent studies in patients undergoing cardiac surgery have pointed towards a possible relationship between the use of aprotinin and postoperative renal failure. First of all, aprotinin is eliminated from the circulation by the kidney. After glomerular filtration, aprotinin is actively reabsorbed by the proximal tubular cells, where it is stored, metabolized and eliminated in 5 to 6 days. Therefore, toxicity to the proximal tubular cells has been suggested as a cause of renal dysfunction postoperatively. Moreover, both authors also suggest that the use of aprotinin increases the risk of thromboembolic events, leading to microemboli in the renal vascularisation and loss of renal function.

The effect of aprotinin has not been studied in great detail in liver transplantation patients, except for a study done by Molenaar et al. including 93 patients. To explore the impact of aprotinin on renal function in this particular patient group, we conducted a two-

center study, including the Royal Free Hospital in London and the University Medical Center in Groningen, using their large prospectively collected databases to allow comparative assessment of renal function in patients who received aprotinin versus those who did not by exacting propensity score stratification and multivariate analyses.

Postoperative renal dysfunction in patients undergoing OLT

Perhaps because of the attention received at the ILTS in 2006, the effect of intraoperative use of aprotinin was discussed in 2007, but solely in abstracts concerning thromboembolic events after OLT, like in 2006. Mahalaxmi Iyer presented the data from Newcastle upon Tyne, concerning the impact of aprotinin on the incidence of hepatic artery thrombosis (HAT). The administering of aprotinin was not associated with an increased incidence of HAT. Mitsuru Nakatsuka et al. reported 2 patients with high doses of aprotinin who had a sudden hemodynamic collapse due to massive intracardiac thrombus formation about ten years ago. Therefore, only small doses of aprotinin are recommended by this author.

The impact of the use of aprotinin on postoperative renal dysfunction was not studied by others. Renal dysfunction and failure are among the most common complications of OLT, with incidences ranging from 12 to 64% and several studies have demonstrated an association between renal failure and increased mortality after OLT. It is, therefore, critically important to establish the impact of aprotinin on the risk of postoperative renal failure after OLT.

Many other authors had renal dysfunction after liver transplantation as topic of their presentation or poster, but in many cases this concerned the development of chronic or late renal failure. Denis Gustin et al. studied predictors of one-year mortality and concluded that kidney injury, and especially severe injury requiring replacement therapy, had worse survival outcome, just as Rogerio Afonso et al. did. Volker Schmitz et al. compared both early and late renal dysfunction and concluded compromised patient survival when early dysfunction developed. Moreover, when looked at postoperative renal dysfunction by other authors, most of them focused on immunosuppression as the main risk factor. Schmitz, for example, found cyclosporine-based immunosuppression to be more disadvantageous as an independent risk factor than tacrolimus.

The introduction of calcineurin-inhibitors (cyclosporine, tacrolimus) significantly improved patient and graft survival after liver transplant. However, side-effects including late onset renal failure are a significant cause of morbidity and mortality. Nora Cejas et al. assessed changes in serum creatinine and glomerular filtration rate following complete withdrawal of cyclosporine or tacrolimus and conversion to sirolimus. This group from Buenos Aires showed that after conversion from the calcineurin-inhibitors to sirolimus in

patients with renal dysfunction, renal function did improve. Moreover, J. Neuberger et al. suggested that the introduction of lower doses of tacrolimus can safely and should be delayed provided the recipient is given daclizumab and mycophenolate mofetil in the immediate postoperative period.

Conclusion

The intraoperative use of aprotinin during liver transplantation continues to be point of discussion. During the meeting in 2006, as well as during this years' meeting, the focus was on the thromboembolic complications after liver transplantation. The abstract I presented concerned renal complications after the use of aprotinin. Given the fact that the relationship between the use of aprotinin intraoperatively and renal function postoperatively has been presented for the first and only time at this years' ILTS meeting, it definitely makes me wonder what next year will bring on this very subject.

N. Warnaar