

Towards Steroid-Free Immunosuppression after Liver Transplantation

Victor M. Zaydfudim¹ and Shawn J. Pelletier²

¹Section of Hepatobiliary and Pancreatic Surgery, Department of Surgery, and ²Charles O. Strickler Transplant Center, University of Virginia, Charlottesville, VA, USA

See "Efficacy and Safety of a Steroid-Free Immunosuppressive Regimen after Liver Transplantation for Hepatocellular Carcinoma" by Qiang Wei, et al. on page 604, Vol. 10, No. 4, 2016

The deleterious long-term side effects and metabolic complications of corticosteroids have inspired initial clinical investigation of corticosteroid withdrawal and avoidance protocols in liver transplantation. The original studies in the 1990s focused on the safety of steroid withdrawal in patients without hepatocellular carcinoma (HCC).^{1,2} Subsequent clinical trials suggested noninferiority of steroid withdrawal and steroid avoidance regimens after liver transplantation in long-term graft function and patient specific outcomes, including survival.³⁻⁵ Recent trials included patients with viral etiologies of chronic liver disease (both hepatitis B and hepatitis C) and HCC, however, data evaluating impact of steroid-free regimens on recurrence in patients transplanted for HCC are less robust. A few single-institution retrospective cohort studies suggested greater tumor recurrence and possibly worse survival in patients with higher dose steroid regimens,^{6,7} however convincing prospective data are insufficient.

The current retrospective cohort study by Wei *et al.*,⁸ examines both posttransplant complications and tumor recurrence in patients with hepatitis B virus (HBV) cirrhosis and HCC. All patients had induction with methylprednisolone; patients in the "steroid-free" group also received basiliximab, while patients in the control group had a 3-month prednisolone taper without basiliximab. All patients in both groups had the same two drug long-term immunosuppression regimen. Importantly, all patients received hepatitis B specific antiviral therapy before and after transplantation. The steroid-free protocol appears to be a paradigm change in this group's practice in 2009 and a 1:2 match control group is selected from noncontemporaneous liver transplant recipients preceding the study group. A few tumor specific metrics in this study are notable. Average pretransplant

α -fetoprotein exceeded 2,000 and $\geq 50\%$ of patients in both steroid-free and control groups had HCC exceeding Milan criteria. Also, while average tumor size was comparable, average tumor number was significantly higher in the earlier patient group managed with a 3-month steroid taper rather than steroid-free protocol.

Posttransplant complications between two groups are similar. While the exact follow-up time for each group is unclear and is theoretically longer for patients managed with 3-month prednisolone taper, proportions of acute rejection, hypertension, new-onset diabetes mellitus, hyperlipidemia, infectious complications, as well as early renal and allograft dysfunction, are similar in both patient groups. Proportion of patients with HBV recurrence is lower in the more contemporaneous steroid-free patient cohort. Survival outcomes are stratified by steroid use and Milan criteria. The authors suggest greater survival among patients within Milan managed with steroid-free protocol, however, lack of direct tumor biology comparisons (α -fetoprotein, tumor size, and tumor number) for these two patient subgroups and noncontemporaneous controls limit direct comparison to steroid-taper patients within Milan criteria.

This study adds another cobblestone on the path towards safe and effective steroid-free immunosuppression in liver transplant recipients. Current data support clinical efficacy of steroid limiting protocols without increased risk of graft loss or dysfunction after liver transplantation. Potentially diminished chance of HBV recurrence with steroid-free regimens is encouraging and tumor-specific survival data requires further investigation. As long-term survival after liver transplantation continues to improve, minimization of steroids is important. In addition to the undesirable metabolic side-effects, long-term steroid use has

Correspondence to: Victor M. Zaydfudim

Department of Surgery, Box 800709, University of Virginia, Charlottesville, VA 22908-0709, USA

Tel: +1-434-924-2839, Fax: +1-434-982-4778, E-mail: vz8h@virginia.edu

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been associated with worse health-related quality of life and psychological disorders in liver transplant recipients.^{9,10} Proliferation of steroid withdrawal, steroid avoidance, and steroid-free immunosuppression protocols should improve long-term patient centered outcomes after liver transplantation.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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