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INVITED COMMENTARY

The question of induction? Maybe not all antibodies are equal …*

Greg J. McKenna and Goran B. Klintmalm

Annette C. and Harold C. Simmons Transplant Institute, Baylor University Medical Center, Transplant Services, Dallas, TX, USA

Correspondence
Goran B. Klintmalm, Annette C. and Harold C. Simmons Transplant Institute, 3410 Worth Street, Suite 950 Dallas, TX 75246, USA. Tel.: +214 820 2050; fax: +214 820 4527; e-mail: gorank@baylorhealth.edu

*Commentary on 'Outcome of induction immunosuppression for liver transplantation comparing anti-thymocyte globulin, daclizumab, and corticosteroid', by Uemura *et al.* [*Transpl Int* 2011; 24: 640].

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Induction immunosuppression has been used for years as a prophylactic strategy to prevent rejection in organ allografts. More specifically, centers have used induction immunosuppression in patients with underlying preoperative renal dysfunction to delay introducing nephrotoxic calcineurin inhibitors and spare renal function.

Despite the fact that induction has been used for decades, there is little definitive evidence of its efficacy in improving patient and graft survival. These data are even more limited in liver transplantation and the current article by Uemura *et al.* [1] in this issue helps to define a role for induction in liver transplantation.

Using induction therapy in liver transplantation highlights several issues specific to livers. The first issue is the rising rate of renal dysfunction in liver transplant recipients. With worsening supply and demand for liver allograft, the average model for end-stage liver disease (MELD) score at transplant is increasing and since renal dysfunction weighs prominently in the MELD score, more liver transplant recipients have renal dysfunction. Induction therapy using antibodies is one of the few effective renal sparing strategies and its use in liver transplantation has tracked the increase in MELD scores, despite the lack of evidence regarding the impact of induction.

What distinguishes induction therapy in liver transplant from other organs such as kidney and heart is that the most common disease etiology for liver transplants – HCV infection – can be potentiated and worsened through the antibody use. HCV infection creates a competing issue: using antibodies such as OKT3 and rATG (rabbit antithymocyte globulin) have been reported to significantly increase HCV recurrence [2,3]; however, using induction therapy to reduce future rejections (known to increase HCV recurrences) should conversely be beneficial. It is important to recognize that context is crucial and we should not extrapolate conclusions in a setting of limited evidence. While OKT3 and rATG have been shown to increase HCV recurrence, this is from its use as a treatment for steroid-resistant rejection. The prolonged duration of therapy required to treat steroid-resistant rejection, as well as its timing later in the post-transplant course beyond the initial first week of

transplant, brings into question the validity of comparing this antibody use to the limited antibody use of induction therapy.

There are several smaller single center trials regarding induction therapy in liver transplantation, but these results have yielded unclear conclusions. Nelson *et al.* using a matched control study of 41 HCV patients showed no survival benefit, but less rejection and more severe HCV recurrence with antibody induction [4]. Levitsky's retrospective study of altuzumab induction in 55 non-HCV patients showed no difference in survival, with a reduction in rejection, however, with an increase in viral infections [5]. Bajjoka *et al.* retrospective study of 118 patients with renal dysfunction treated with rATG and delayed calcineurin inhibitor showed no difference in survival, with possibly lower rejection and no impact on HCV recurrence [6]. Eason *et al.* randomized trial of 120 patients comparing steroid-free rATG to steroids also found no difference in survival with fewer rejection episodes using rATG and no clear impact on HCV recurrence [7]. The common themes of these single center studies are improvements in rejection episodes but with no real impact on overall survival and possible negative impact on viral infections including HCV.

The HCV-3 Study was a large, multicenter randomized trial of 312 liver transplant recipients that assessed the impact of the IL-2R binding monoclonal dacluzimab followed by steroid-free maintenance immunosuppression [8]. The 2-year analysis shows no difference in survival, acute rejection, and no difference in HCV recurrence. The 2-year analysis of this large dataset is submitted for publication.

The various studies do not show a clear survival benefit; however, all of them only evaluate short-term survival at 1 year, and survival benefits might not become obvious until many years later. In the same way, the impact on HCV recurrence may not necessarily be obvious at 1 year and may require several years of observation. It is for this reason that data from the large UNOS and SRTR databases may be the key to obtain the long-term data and large population needed. In this journal issue, the study from Uemura *et al.* [1] examine the UNOS database in an attempt to determine the outcome of induction immunosuppression in liver transplantation using large populations and longer-term data to make conclusions.

In the past year, there have been several reviews of the UNOS database on induction, with each one elucidating more details on the subject. Cai and Terasaki's [9] UNOS database review from 2003 to 2009 of induction therapy in all organ transplants found significant improvement in graft survival (68% vs. 64%, $P < 0.001$) and patient survival (73% vs. 70%, $P < 0.001$) at up to 5 years post-transplant and found lymphocyte depleting antibodies to be superior than non-depleting antibodies for graft survival. Moonka's [10] UNOS database review from 1987 to 2008 showed improved patient survival at 5 years with induction therapy for both HCV-positive patients (70.8% vs. 68.7%, $P < 0.001$) and HCV-negative patients (78.8% vs. 76.7%).

Uemura *et al.* [1] have built upon these earlier reports with their study of the UNOS database looking particularly at HCV patients, assessing the impact of the different types of induction therapies on outcomes in liver transplantation, comparing the lymphocyte-depleting monoclonal antibody rATG (with and without steroids) to the CD-25 specific non-lymphocyte depleting antibody dacluzimab and also to steroid induction. Looking at all liver transplant recipients combined, there was no difference in patient survival or graft survival between the rATG group, dacluzimab group and steroid group at up to 5 years. However, when only the HCV patients were examined, clear differences appear depending on the antibody used. Patient survival with dacluzimab induction compared with rATG and to steroids was significantly higher at 1 year (92% vs. 86% vs. 88%) and 5 years (77% vs. 64% vs. 70%) and graft survival was also significantly increased with dacluzimab. Uemura *et al.* [1] hypothesize that this improved survival outcome using dacluzimab in HCV patients may be a function of avoiding lymphocyte depletion. Rosen *et al.* [11] have shown that good proliferative T-cell response to HCV antigens is important in preventing HCV recurrence, thus avoiding T-cell depletion with dacluzimab when compared with rATG might be a factor in the improved long-term survival.

Perhaps with induction therapy in liver transplantation, it may be that ''one size does not fit all''. While avoiding rejection is important in HCV patients to limit HCV recurrence, in non-HCV patients a rejection episode does not carry the impact on survival with liver transplant that it does in other organ transplants. The lack of a clinically relevant survival benefit in non-HCV patients using induction therapy may not warrant the large expense associated with routine antibody induction for rejection prophylaxis. Given the growing indications for renal sparing strategies, however, induction therapy is still needed and in non-HCV patients, induction using lymphocyte-depleting antibodies such as rATG may be most effective at renal-sparing. In HCV patients, using a non-lymphocyte depleting CD-25 antibody such as dacluzimab may offer the best compromise at maximizing survival with renal sparing strategies. It is ironic, however, that despite this data showing benefit with dacluzimab in HCV patents, that dacluzimab has ceased to be produced and is not available. Hopefully another CD-25 specific antibody such as basiliximab will pose a similar benefit when it is used in HCV patients.

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