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INVITED COMMENTARY

Donor-specific alloantibodies in liver transplantation: how should we define and improve long-term success?

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How should we define "success" in liver transplantation, and who should make that determination? Should "success" be measured by 1-year, 5-year, or >20-year outcomes? Should regulators, practitioners, or pediatric recipients determine this? Should these outcomes be available to everyone or only when it is cost-effective? Although significant short-term outcome improvements have been accomplished, long-term (>10-year) survival has remained relatively unchanged (54% based on the Scientific Registry of Transplant Recipients [1]). Therefore, it is critical to develop new ways to improve long-term outcomes, ideally with the help of serum-based biomarkers, and donor-specific alloantibodies (DSA) are one of the many potential biomarkers being evaluated.

Fortunately, it is no longer debated that DSA in serum can be associated with liver allograft injury and loss [1]. However, the rarity of DSA persistence post-transplant [2] combined with DSA's imperfect correlation with short-term adverse outcomes and cost of testing has resulted in the absence of DSA testing in standard clinical care. Therefore, Del Bello and colleagues, in this edition of Transplant International [3], should be commended for their single-center prospective single antigen bead testing at 1, 3, 6, and 12 months, yearly, and at the time of abnormal liver function testing (LFT) of 152 adult liver allograft recipients devoid of pretransplant DSA with >1-month survival. This male predominant group was assessed for *de novo* DSA defined as a mean fluorescence intensity (MFI) ≥1000.

They showed, similar to prior reports [4,5], that risk factors for *de novo* DSA formation include young age and low levels of and noncompliance with immunosuppression. Del Bello and colleagues also found a univariate but not multivariate association between immunosuppression (cyclosporine) and *de novo* DSA formation, this combined with other reports highlights the important role of immunosuppression in *de novo* DSA prevention—the preferred approach compared to treatment [4,6]. Fortunately, their more frequent DSA testing allowed for more precise

determination of *de novo* DSA development; the highest risk period occurred during the first year (62%, 13/21) with almost half of the *de novo* DSA in the first year occurring <1 month after transplant. During this first year, the risk for *de novo* DSA has been relatively consistent among studies (8.1–9.3%), with the exception of the Mayo Clinic experience where no *de novo* DSA was seen in the first year, further highlighting the likely role of immunosuppression early after transplant as the Mayo Clinic used triple immunosuppression with tacrolimus, mycophenolate, and steroids [3,4,7]. This important timing of *de novo* DSA development educates us about more than DSA; it likely confirms the highest risk immunologic period after transplant as DSA may in fact be a biomarker of alloimmune reactivity.

Roughly half of the *de novo* DSAs were detected at the time of abnormal LFTs: 82% (9/11) had antibody-mediated rejection (AMR) most of which was combined with T-cell-mediated rejection, although 52% (11/21) of all patients with *de novo* DSA had or developed some type of rejection. The criteria used to diagnose acute AMR in this report descriptively was according to current standards [8,9], although the high rate of acute AMR this far after transplant and the absence of T-cell-mediated rejection in two cases were both very surprising.

The other roughly half of *de novo* DSAs were detected on routine screening. These patients all underwent a single liver biopsy, and none had any type of rejection found. However, the mean MFI for these patients was <5000, none were C1q positive, and 42% (5/12) became undetectable after a median of 7 months. Although C1q positivity was not statistically significantly associated with AMR, there was a trend ($P = 0.1$). Another larger report showed C1q positivity, but more importantly IgG3 subclass positivity, was more strongly associated with adverse outcomes than standard DSA positivity alone [10]. However, it is critical to note that follow-up liver biopsies were not performed to determine whether fibrosis progression occurred, which is a concern given other group's findings [11–15]. In addition, the emerging concept of chronic AMR [16], with more subtle findings that can occur even in patients with normal LFTs, was not part of their histologic evaluation. This is especially critical because C4d testing is less sensitive in patients with chronic than acute AMR [8,16].

Del Bello and colleagues should also be commended for their acute AMR treatment efforts that achieved short-term "success" in 66% (6/9) of patients. This likely results from early diagnosis; however, the definition of success was normal LFTs, which although comforting to patients and practitioners cannot be seen as success when DSA is present. Fortunately, 56% (5/9) of patients after AMR treatment had a MFI <1000, although without follow-up liver biopsy one cannot be sure it is not all in the graft. In addition, the lack of a uniform protocol, the absence of prespecified end points, and the paucity of follow-up histology highlights our need for prospective multicenter treatment trials. It is clear that the rarity of AMR, especially acute, will never allow a single center to elucidate the best therapeutic strategy. In fact, this will only be accomplished through: (i) uniform and stringent diagnostic criteria with high specificity, (ii) single antigen bead testing of all patients with rejection with either (a) histologic features of AMR [8] or (b) steroid resistance, (iii) large multicenter collaborations committed to testing protocolized AMR therapy with prespecified short-term end points, and (iv) a commitment to follow these patients with long-term protocol liver biopsies. This is of critical importance in acute AMR, but even more salient in the next great frontier of chronic AMR [16] that will likely prove more indolent but more prevalent and result in a greater impact on overall graft survival, that is, if >10-year graft survival is your definition of success.

Ultimately, we have learned that DSA testing is critical to early diagnosis and treatment of AMR in patients with abnormal LFTs and either histologic features of AMR or steroid resistance. However, the true utility and cost-effectiveness of protocolized DSA testing in patients with normal LFTs remains to be determined. To improve long-term outcomes after liver transplantation, we must develop biomarkers of alloimmune reactivity that facilitate personalized immunosuppression minimization. Toward that goal, DSA needs to be rigorously prospectively tested as one such possibility.

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