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Bortezomib: A New Promising Therapy for Early Antibody-Mediated Rejection After Liver Transplantation?

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Antibody-mediated rejection (AMR) after ABO-compatible (ABOc) liver transplantation (LTx) is a rare phenomenon. When compared with ABOc LTx, ABO-incompatible (ABOi) LTx is related to a higher incidence of complications, especially AMR, hepatic artery thrombosis, and also biliary complications.[1] ABOi LTx is usually accomplished through living liver donation and rarely performed in the Western World. However, ABOi LTx is a relatively common of practice in Eastern countries where deceased donation is scarce.

As a preparation to ABOi LTx, plasmapheresis (PP) or immunoadsorption with low-dose intravenous immunoglobulin (IVIG) replacement is usually necessary in order to lower anti-A and anti-B antibodies against the potential live donor. The CD20 inhibitor rituximab is also utilized along PP.[2]

Most rejection episodes following ABOc are cellular rejections. The liver allograft is relatively resistant to humoral response. Thus, AMR following ABO-c LTx is exceedingly rare.[3,4] Some of the AMR following ABOc LTx cases are secondary to anti-HLA antibodies in positive XM LTx cases.[3]

The diagnosis of AMR following ABOc LTx is challenging. In this setting, AMR is usually triggered by anti-HLA antibodies. However, due to the rarity of AMR in the setting of ABOc LTx, most groups do not perform pre-LTx crossmatch. In LTx recipients, AMR may have a variety of clinical presentations, including one or more of the following: elevation of liver enzymes, hepatic artery thrombosis, or even biliary complications. AMR is diagnosed by the following 3 criteria: (1) clinical signs of graft dysfunction, (2) histopathology indicative of acute injury ± positive C4d stain, and (3) presence of HLA donor-specific antibodies (DSA) or anti-A/anti-B antibodies.

The standard management of AMR following kidney transplantation (KTx) (either ABOc or ABOi) relies on PP or immunoadsorption with IVIG along with rituximab.[3] This therapy is driven to both reduce the burden of circulating anti-HLA antibodies and limit their production. Although this management is usually successful for AMR following KTx, its efficacy in the setting of AMR following LTx seems controversial.[3,4] Ronstron et al[4] obtained complete control of AMR employing PP and rituximab. Conversely, Chan et al[3] were not able to rescue any of the 2 patients treated with PP and rituximab. Similar findings were reported by Lee et al[5] for 3 patients. Moreover, all these patients experienced death following loss of the liver allograft.[3,5]

Bortezomib inhibits the chymotrypsin-like site of the 20S proteolytic core within the 26S proteasome, thereby inducing cell-cycle arrest and apoptosis on plasma cells. There have been few reports of the use of bortezomib as a treatment for AMR following ABOc LTx. Paterno et al[6] reported on 3 cases of successful treatment of AMR following ABOc LTx by bortezomib. Chan et al[3] and Koch et al[7] described 1 additional case each. In the latter case, bortezomib was able to rescue an AMR episode that was resistant to splenectomy. Lee et al[5] described the largest series of bortezomib utilization for refractory AMR after ABOc LTx. The authors achieved AMR control in 3 out of the total 6 patients receiving this approach (including 1 case of AMR secondary to ABOi LTx). The remaining 3 patients lost their liver allografts and experienced a fatal outcome.[5]

In this issue of *Transplantation Direct*, Tajima et al[8] report on the use of bortezomib as a successful treatment for early refractory AMR after ABOi LTx in an adult patient. The authors were not able to obtain control of the AMR with readministration of rituximab, steroid-pulse, IVIG, and PP in the posttransplant period. Only after adding bortezomib on posttransplant day 9, the authors obtained complete resolution of the AMR episode. Of note, bortezomib achieved a fast and intense reduction of CD19/20 cells and antibody titers at an early stage after LTx, being introduced only after therapies were not able to control the humoral response.

Before the report of Tajima et al, there was only 1 prior case reporting the use of bortezomib for the treatment of AMR in an ABOi LTx recipient.[5] The drug was also able to control

Received 22 June 2019. Revision received 13 July 2019.

Accepted 18 July 2019.

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M.F.C. and E.R. participated in research design and writing of the article.

The authors declare no funding or conflicts of interest.

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ISSN: 2373-8731

Transplantation Direct 2019;5: e492; doi: 10.1097/TXD.0000000000000931. Published online 23 September, 2019.

rejection in that prior literature case. Thus, the importance of the report of Tajima et al resides on both its rarity and its successful outcome. Although there are no randomized controlled trials of bortezomib in early AMR either in KTx or LTx, some KTx studies comparing bortezomib use to treat AMR versus a control group have shown higher AMR successful treatment rates, better kidney graft survival, and improved renal function for the KTx patients who received bortezomib.[9]

From the KTx studies, we would highlight 2 issues that could be extrapolated to LTx and, specifically, to the Tajima et al reported case. First, KTx recipients with early posttransplant AMR were more likely to have a better response to bortezomib therapy than those with late AMR episodes.[10] Second, desensitization studies have shown a limited efficacy of bortezomib monotherapy to reduce DSA. By contrast, bortezomib contributed significantly to reducing DSA associated with other therapies such as PP, rituximab, steroids, and/or IVIG.[9] Adding bortezomib to PP, IVIG, steroids, and rituximab could be a good option for treating early AMR both in ABOc and ABOi LTx.

Due to its rarity and variety of clinical presentations, AMR following ABOc may be misdiagnosed or diagnosed too late in its course. Otherwise, maybe some cases of suspected AMR were indeed some other diagnosis, and therefore did not respond to antirejection treatment. Those difficulties might be 1 reason for the inconsistent effects of therapy for AMR in this setting.

Unlike KTx, in which graft loss may be treated with dialysis, failure of the liver allograft is a catastrophic event that results in patient death unless a deceased donor becomes readily available. In several of the reports cited above, liver allograft failure was followed by patient death. Thus, AMR following LTx is an event of high lethality.

Based solely on small case series and single case reports, it seems that the use of bortezomib might be effective for AMR refractory to the standard management (PP with rituximab) both in ABOc and ABOi LTx, although not all patients responded to this therapy.[5] Perhaps some of these failures could be attributed to delayed start of the drug. Thus, bortezomib should be considered as a potential option in every case of AMR after LTx.

REFERENCES

1. Lee EC, Kim SH, Park SJ. Outcomes after liver transplantation in accordance with ABO compatibility: a systematic review and meta-analysis. *World J Gastroenterol.* 2017;23(35):6516–6533.
2. Lee J, Lee JG, Lee JJ, et al. Results of ABO-incompatible liver transplantation using a simplified protocol at a single institution. *Transplant Proc.* 2015;47(3):723–726.
3. Chan KM, Lee CS, Wu TJ, et al. Clinical perspective of acute humoral rejection after blood type-compatible liver transplantation. *Transplantation.* 2011;91(5):e29–e30.
4. Rostron A, Carter V, Mutunga M, et al. A case of acute humoral rejection in liver transplantation: successful treatment with plasmapheresis and mycophenolate mofetil. *Transpl Int.* 2005;18(11):1298–1301.
5. Lee CF, Eldeen FZ, Chan KM, et al. Bortezomib is effective to treat acute humoral rejection after liver transplantation. *Transplant Proc.* 2012;44(2):529–531.
6. Paterno F, Shiller M, Tillery G, et al. Bortezomib for acute antibody-mediated rejection in liver transplantation. *Am J Transplant.* 2012;12(9):2526–2531.
7. Koch M, Gräser C, Lehnhardt A, et al. Four-year allograft survival in a highly sensitized combined liver-kidney transplant patient despite unsuccessful anti-HLA antibody reduction with rituximab, splenectomy, and bortezomib. *Transpl Int.* 2013;26(8):e64–e68.
8. Tajima T, Hata K, Okajima H, et al. Bortezomib against refractory antibody-mediated rejection after ABOincompatible living-donor liver transplantation: dramatic effect in acutephase? *Transplant Direct* [In Press].
9. Waiser J, Budde K, Schütz M, et al. Comparison between bortezomib and rituximab in the treatment of antibody-mediated renal allograft rejection. *Nephrol Dial Transplant.* 2012;27(3):1246–1251.
10. Walsh RC, Brailey P, Girnita A et al. Proteasome inhibitor-based antihumoral therapy: differential response in early vs. late antibody mediated rejection. *Transplantation* 2011;91:1218–1226.