ISHLT JOURNAL WATCH
August 2023 | Pharmacy

Krystal Walter, PharmD, BCTXP
Michigan Medicine, Ann Arbor, MI USA

Victoria Reams, PharmD, BCTXP
EDITOR

ISHLT.ORG

Tocilizumab for Antibody Mediated Rejection Treatment in Lung Transplantation

January SE et al. *J Heart Lung Transplant*. 2023;S1053-2498(23)0186601.

Study Highlights

Overview: Tocilizumab (TCZ) is an interleukin-6 (IL-6) inhibitor used for chronic antibody mediated rejection (AMR) in kidney transplant; use in lung transplant recipients (LTRs) has not been reported

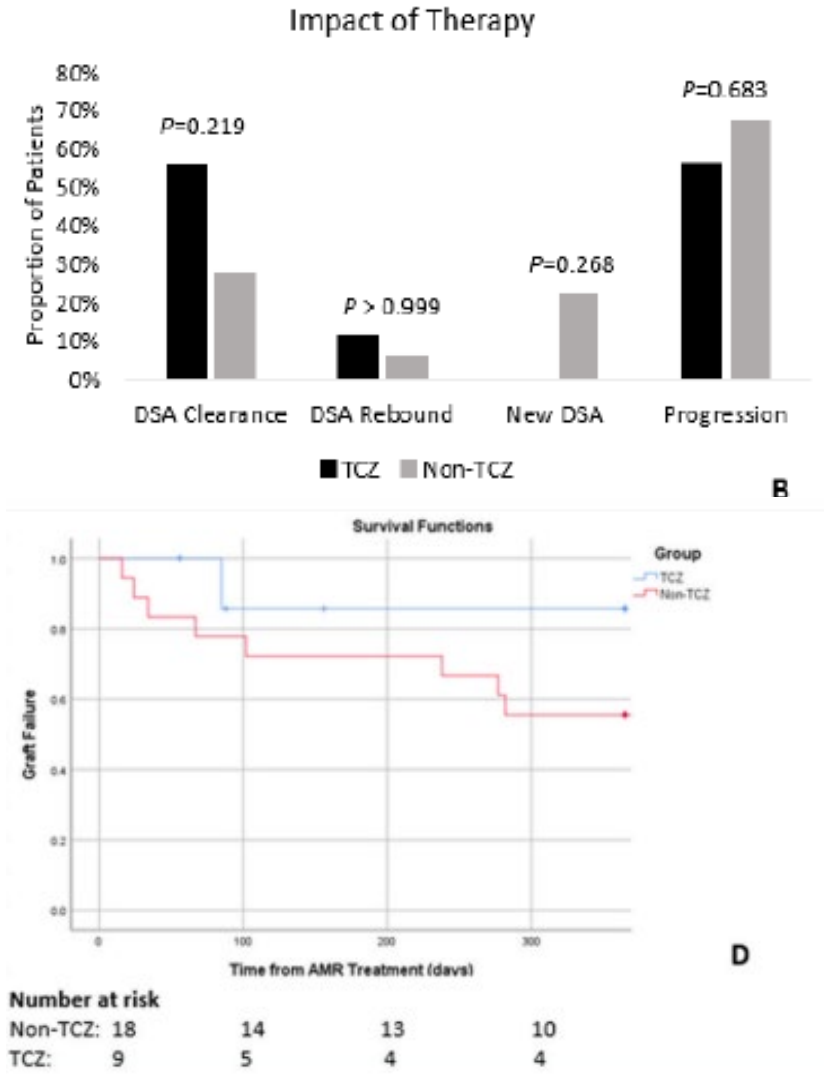
Methods: Retrospective single center study of adult bilateral LTRs after 1/1/2011 with HLA DSA + AMR; stratified by treatment regimen

- TCZ 8 mg/kg monthly (max 800 mg/dose) vs non-TCZ-based regimen
- **TCZ**: TCZ + IVIG (3); TCZ + rATG + CFZ (4); TCZ + CFZ + IVIG (1); TCZ + ECP + IVIG (1)
- **Non-TCZ**: RTX (17) +/- CFZ/BTZ (6) +/- rATG (8) +/- IVIG (17) +/- PLEX (1) based regimens

Results: Reported as TCZ (n=9) vs non-TCZ (n=18)

- FEV1: 1.24 L vs 1.45 L P=0.686
- FVC: 1.9 L vs 2.08 L p=0.818
- Graft failure: 11.1% vs 50%, p=0.049
- Post treatment infections: 56% vs 61%
- ↑ liver enzymes: 2 in each group (self resolved)

Conclusion: Compared to a non-TCZ containing AMR treatment regimen, TCZ demonstrated a favorable trend in terms of DSA clearance, incidence of recurrent/new DSA, and graft failure with a similar safety profile



Reviewer's Comments

- This study demonstrates the potential role of TCZ in the treatment of AMR in which the majority of LTRs had class II DSA
- TCZ was compared to a primarily rituximab-based AMR treatment regimen
- TCZ used both solely with IVIG as well as in combination with B and T cell depleting agents (proteasome inhibition and/or thymoglobulin)
- Lack of plasmapheresis in tocilizumab group differs from typical AMR treatment regimens
- Should consider potential cost considerations and barriers for obtaining this agent in the outpatient setting ~44% remained on TCZ monthly at end of follow-up)
- Future research is needed to determine the utility of TCZ on AMR treatment outcomes

Limitations

- Small sample size
- Lack of extended follow-up duration
- Significant variability in treatment regimens existed between two groups making it difficult to ascertain impact of TCZ alone on AMR treatment

ISHLT JOURNAL WATCH
August 2023 | Pharmacy

Ashley Postell, PharmD, BCPS
Mayo Clinic, Jacksonville, FL USA

Victoria Reams, PharmD, BCTXP
EDITOR

ISHLT.ORG

First Use of Imlifidase Desensitization in a Highly Sensitized Lung Transplant Candidate: A Case Report

A. Roux et al. *Am J Transplant* Jan 2023 doi:10.1016/j.ajt.2022.11.025

Study Highlights

Objective: Access to donor organs is reduced for patients with preformed donor specific antibodies (DSAs) due to the increased risk of hyperacute rejection, antibody medicated rejection (AMR), and chronic lung allograft dysfunction (CLAD). Despite current desensitization options, there is a persistent need for novel therapies. This case report presents the first use of imlifidase for DSA depletion prior to bilateral lung transplant (BOLT).

Case Description: 48-year-old male was listed for BOLT secondary to pulmonary fibrosis and chronic hypersensitivity pneumonitis. Virtual panel reactive antibodies (vPRA) was 92% and 85% using a mean fluorescence intensity (MFI) cutoff of 5,000 and 10,000, respectively.

Perioperative desensitization: Imlifidase 0.25 mg/kg was administered prior to a donor offer that was unable to be transplanted (day -7). A second dose of imlifidase was administered prior to the second graft offer (day 0). Additional desensitization therapies were administered per Figure B.

Postoperative Course: After the first imlifidase dose, vPRA was reduced to 40.9% and 0% using an MFI cutoff of 5,000 and 10,000, respectively. vPRA returned to baseline by day 7 post-dose. Biopsies at 3 days, 2 weeks, and 1 month were negative for acute cellular rejection (ACR) or AMR.

Conclusion: Imlifidase was safe and allowed a successful BOLT in a highly sensitized patient. Imlifidase may be an option for patients who previously failed desensitization strategies.

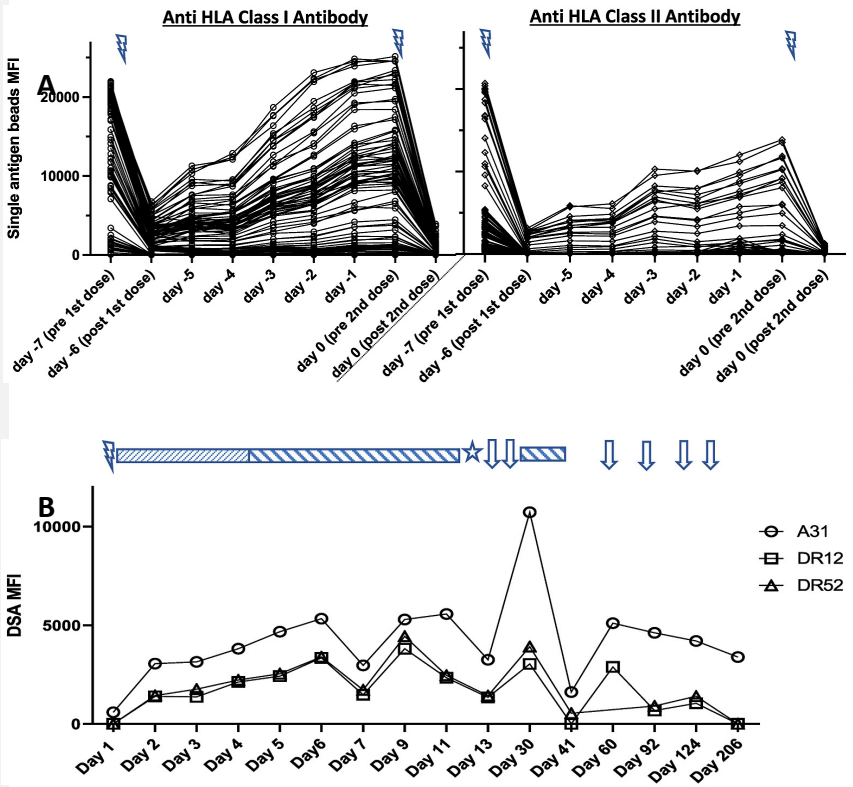


Figure Legend: A) Change in HLA Class I and II single antigen MFI preoperatively and B) Change MFI of DSAs postoperatively

Reviewer's Comments

- Imlifidase was previously shown to convert 90% of positive crossmatches to negative in kidney transplant recipients with a median cPRA of 99.83% (Jordan SC, et al. *Transplantation*. 2021). This is the first case report describing a successful use of imlifidase prior to lung transplantation.
- Imlifidase rapidly depleted all IgG antibodies including DSAs, but antibody rebound occurred 7 days after administration
- Imlifidase cleaves all subclasses of IgG – including monoclonal antibodies. Note the following recommendations for spacing imlifidase and transplant medications.

Time Interval after Imlifidase Administration	No Time Interval Needed	12 Hours	4 Days	1 Week
Medication	• Equine anti-thymocyte globulin • Eculizumab	• IVIG	• Alemtuzumab • Basiliximab • Rituximab • Rabbit anti-thymocyte globulin	• Belatacept

Limitations

- Inherent limitations of a case report
- Imlifidase was used in combination with a C1 inhibitor, plasmapheresis, rituximab, IVIG, and alemtuzumab. No data on use of imlifidase monotherapy or when administered in a differing sequence.

ISHLT JOURNAL WATCH
August 2023 | Pharmacy

Daryl Nnani, PharmD, BCTXP
Montefiore Medical Center, Bronx, NY USA

Victoria Reams, PharmD, BCTXP
EDITOR

ISHLT.ORG

Three-year post heart transplant outcomes of desensitized durable mechanical circulatory support

Youn, J et. al. (2023). *Journal of Heart and Lung Transplantation*. | https://doi.org/10.1016/j.healun.2023.05.001

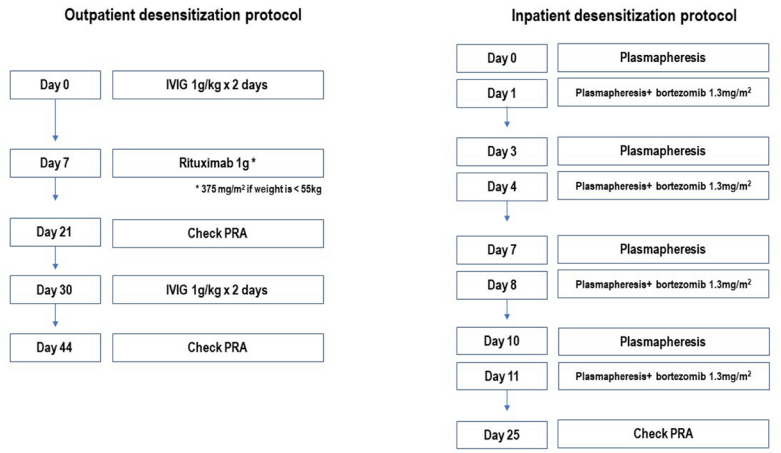
Study Highlights

Objective: To investigate the post-transplant outcomes of desensitized MCS patients compared to desensitized non-MCS and all desensitized (DST) patients

Methods: Single-center prospective, observational analysis of 689 consecutively enrolled HTX recipients between 2010 and 2016. Patients were categorized into three groups, group A (21 desensitized MCS patients), group B desensitized (28 non-MCS patients), group C (640 non-desensitized group). Outpatient desensitization protocol consisted of IVIG 1 g/kg x 2 days and Rituximab 1 gram (375 mg/m^2 if < 55kg). Inpatient desensitization protocol consisted of plasmapheresis and bortezomib 1.3 mg/m^2. Post-transplant outcomes evaluated included PGD, 3-year patient survival, NF-MACE, freedom from CAV, any treated rejection, ACR, AMR , and infectious complications.

Results: Study participants in group A exhibited significantly greater pre-DST PRA and higher PRA reduction post-DST than group B.

Conclusion: DST in MCS patients significantly reduced PRA resulting in expanding the donor pool. DST MCS patients exhibited similar clinical outcomes to non-desensitized control patients in the same study period



Outpatient and Inpatient Desensitization Protocol

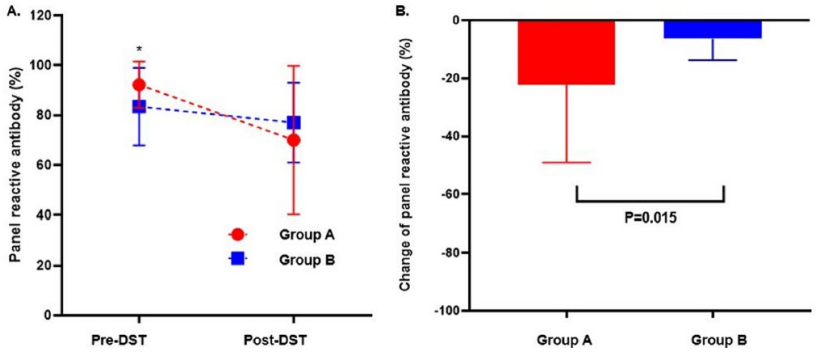


Figure 2A: Change in PRA Pre-DST and Post-DST in Group A & B
Figure 2B: PRA Reduction Post-DST in Group A & B

Reviewer's Comments

- This study adds to an area in which there is a paucity of data providing information on DST in patients requiring MCS
- Would have liked to see an evaluation of outcomes in transplant recipients who did not undergo HTx when comparing safety and efficacy of DST
  - There may be a higher incidence of mortality in desensitized MCS patients awaiting transplant
- Information on the duration of MCS and whether sensitization is pre- or post-MCS implantation
- 1-year outcomes would have been of interest as the effects of many of the DST and induction strategies due not extend well beyond 1 year

Limitations

- Conducted at a single center
- Small sample size reduces generalizability
- DST protocols were not standardized as some patients underwent repeated DST
- The study only included MCS patients who underwent HTx. Did not analyze patient outcomes of DST MCS patients who did not undergo HTx
- No information regarding the presence of DSA, non-HLA antibodies, C1q or CXM

ISHLT JOURNAL WATCH
August 2023 | Pharmacy

Sara Farghaly, PharmD, BCTXP
Montefiore Medical Center, Bronx, NY USA

Victoria Reams, PharmD, BCTXP
EDITOR

ISHLT.ORG

A randomized controlled trial of presatovir for respiratory syncytial virus after lung transplant

Gottlieb, J et. al. JHLT July 2023 | https://doi.org/10.1016/j.healun.2023.01.013

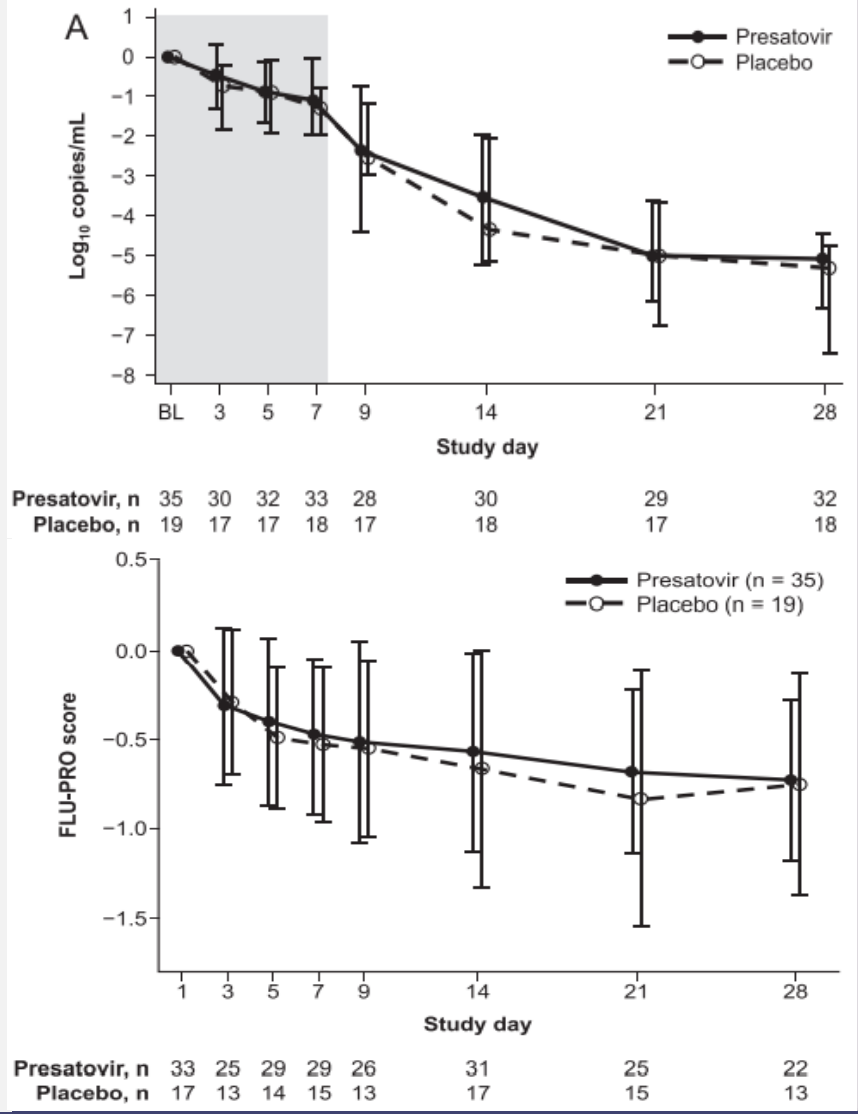
Study Highlights

Background: Treatment modalities for respiratory syncytial virus (RSV) are limited to ribavirin, intravenous immunoglobulin, and supportive care.

Objective: Evaluate the efficacy and safety of presatovir, a fusion inhibitor, for the treatment of RSV.

Methods: Phase 2b, randomized, double-blind, placebo-controlled trial. Patients received Presatovir 200 mg PO on day 1 followed by 100 mg PO daily on days 2-14 OR placebo. Lung, or heart/lung transplant patients were included. Patients with rapidly deteriorating graft function for any reason, or respiratory coinfection within 14 days of screening were excluded.

Results: 111 patients were screened; 61 were randomized. There was no difference in time-weighted RSV viral load from baseline to day 7 between the two groups (difference= 0.10 $\log_{10}$ copies/mL, CI: -0.69-0.46; p=0.72). There was no difference in time-weighted average change in patient reported outcome measures (FLU-PRO) (difference=0.01, CI:-0.12-0.15;p=0.86).



Reviewer's Comments

This study evaluated the efficacy and safety of presatovir in lung transplant patients with RSV and found no benefit in its use. A previous study in healthy adults had shown the administration of presatovir to be beneficial, therefore its use in transplant patients may be hindered by immunosuppression. While the drug did not demonstrate significant benefits, the authors of the study highlighted its importance in providing valuable insights and laying the groundwork for future research in evaluating these therapies for this at-risk population.

Limitations

- Median time to presatovir administration was 6-days post symptom onset with the virus exhibiting a peak viral load at approximately 5 days post exposure in healthy adults. Consequently, it remains uncertain whether administering the drug earlier than 6 days could have conferred greater benefit.
- The degree of immunosuppression in these patients is unknown which may have played a significant role in influencing their response to treatment.

Conclusion

There was no benefit in using presatovir for treatment of RSV in lung transplant patients.