Clinical Utility of 1:16 Serum Dilution as a Predictor of Response to Therapeutic Plasma Exchange For HLA Antibody-Mediated Rejection Treatment And Overall Survival in Lung Transplant Recipients: A Two Center Study

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Abstract

Background: Antibody-Mediated Rejection (AMR) due to HLA donor-specific antibodies (DSA) is associated with poor outcomes in lung transplant recipients (LTR). Successful AMR treatment using therapeutic plasma exchange (TPE) improves clinical outcomes in LTR. The objective of this study was to assess the clinical utility of 1:16 serum dilution HLA antibody test results as a predictor of response to TPE for AMR treatment in LTR.

Methods: A retrospective analysis of 21 LTR diagnosed with AMR due to de novo HLA DSA (dnDSA) and successfully treated with TPE was performed at Mayo Clinic (n = 7) and Temple University Hospital (n = 14). HLA antibodies were detected by Luminex single antigen beads assay. Mean Fluorescence Intensity (MFI) levels were measured before the 1st and after the 5th TPE session using undiluted and 1:16 diluted sera. Statistical analysis was performed using IBM® SPSS® Statistics (v26; Armonk, NY).

Results: Of 21 patients, 9 and 12 patients were diagnosed with early (< 3 months post-transplant) and late (6 months – 3 years post-transplant) AMR respectively. All patients R and late AMR, respectively also had class I dnDSA. The MFI for all positive dnDSA in 1:16 diluted sera collected before 1st TPE demonstrated a significant correlation with MFI in undiluted sera collected 1 day after 5th TPE in both early (Fig. 1A; R^2 = 0.8786) and late (Fig. 1B; R^2 = 0.9045) AMR post-transplant. In addition, reduction in MFI of dnDSA in 1:16 diluted sera correlated with better overall LTR survival following TPE (Fig, 2; p = 0.01).

Conclusion: The MFI of 1:16 serum dilution before 1st TPE may be utilized as a surrogate to predict response to TPE for AMR treatment and overall survival in LTR.

Objectives

Assess the clinical utility of 1:16 serum dilution HLA antibody test results as a predictor of response to TPE for AMR treatment in LTR.

Methods

Study Subjects and Sample Sources: A retrospective analysis of 21 LTR diagnosed with AMR due to de novo HLA DSA (dnDSA) and successfully treated with TPE was performed at Mayo Clinic (n = 7) and Temple University Hospital (n = 14). All patients were assessed and monitored pre-and post transplant for the presence of HLA antibodies per institutional protocol. Inclusion criteria included all primary and repeat heart transplant recipients that were > 18 years old irrespective of gender and race. Recipients who did not survive the intra-operative period during heart transplant surgery or recipients undergoing multiorgan transplantation were excluded from the study. Demographic and clinical information (age, gender, ethnicity, smoking history, patient underlying heart disease diagnosis, comorbidities), immunosuppression therapy, HLA lab test results (HLA antibodies and crossmatch results), and date of death whenever applicable was obtained from the medical records.

HLA antibody detection: Recipient serum samples were treated with EDTA to avoid the prozone effect. Sera were tested for IgG antibodies against HLA class I and II using the LABScreen single antigen beads (One Lambda-ThermoFisher, Inc.). The presence of HLA DSA against HLA-A, -B, -C, -DRβ, -DQα/β, and -DPβ antigens was determined. HLA DSA were defined as having a Mean Fluorescence Intensity (MFI) of more than 1000. The MFI levels were measured before the 1st and after the 5th TPE session using undiluted and 1:16 diluted sera. Statistical analysis was performed using IBM® SPSS® Statistics (v26; Armonk, NY).

Correlation between de novo DSA in undiluted and 1 : 16 diluted sera before and after TPE

Fig. 1A

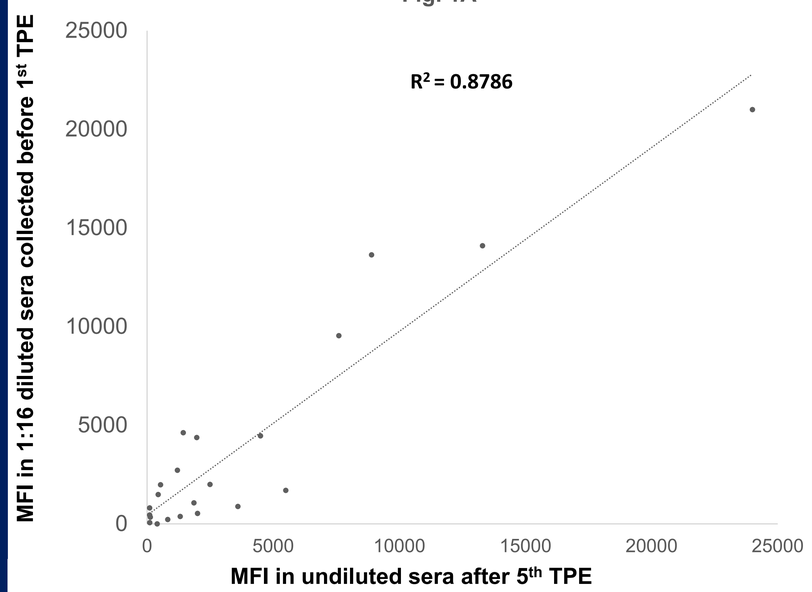

Fig. 1B

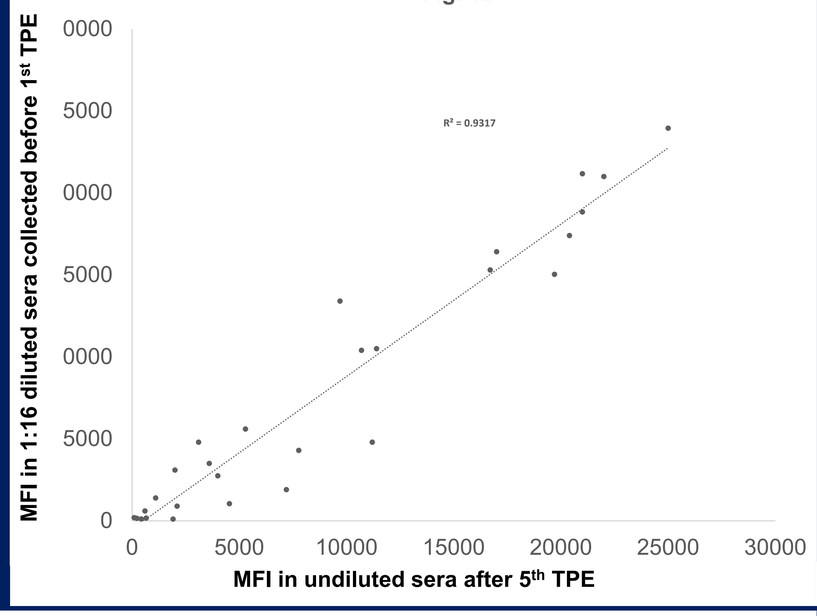

Figure 1: MFI levels of HLA antibodies were measured before the 1st and after the 5th TPE session using undiluted and 1:16 diluted sera in (A) early (< 3 months post-transplant) and (B) late (> 6 months post-transplant) AMR.

Correlation between reduction in de novo DSA and LTR survival post TPE

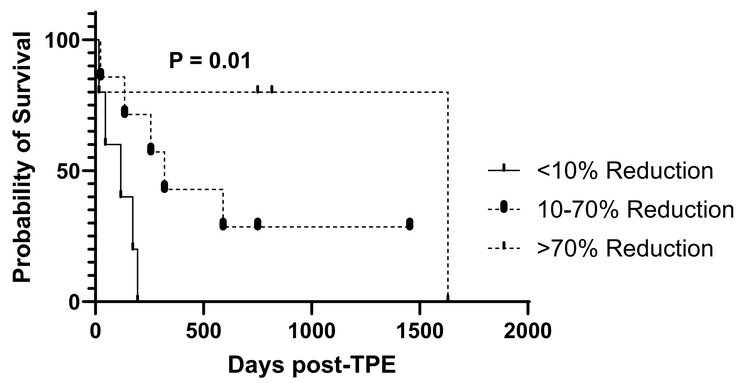

Figure 2: Correlation between reduction in MFI of dnDSA in 1:16 diluted sera and overall LTR survival following TPE

Results

1) **Of 21 patients, 9 and 12 patients were diagnosed with early (< 3 months post-transplant) and late (6 months – 3 years post-transplant) AMR respectively.**
2) **All patients had Class II dnDSA. In addition, 55% and 16% of LTR with early AMR and late AMR, respectively also had class I dnDSA.**
3) **The MFI for all positive dnDSA in 1:16 diluted sera collected before 1st TPE demonstrated a significant correlation with MFI in undiluted sera collected 1 day after 5th TPE in both early (Fig. 1A; R^2 = 0.8786) and late (Fig. 1B; R^2 = 0.9045) AMR post-transplant.**
4) **Reduction in MFI of dnDSA in 1:16 diluted sera correlated with better overall LTR survival following TPE (Fig, 2; p = 0.01).**

Conclusion

The MFI of 1:16 serum dilution before 1st TPE may be utilized as a surrogate to predict response to TPE for AMR treatment and overall survival in LTR.

References

1) **Timofeeva OA, Alvarez R, Pelberg J, Yoon E, Alsammak M, Geier SSet al. : Serum dilutions as a predictive biomarker for peri-operative desensitization: An exploratory approach to transplanting sensitized heart candidates. Transpl Immunol 2020;60:101274.**
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