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Combination, Sequential Therapies Incorporating Tocilizumab Decrease the Progression of Chronic Lung Allograft Dysfunction (CLAD) after Lung Transplantation: Initial Clinical Experience

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Abstract

Introduction: TH-17 and IL-6 interactions and detrimental biologic effects have been shown in rodent models of Chronic Lung Allograft Dysfunction (CLAD). Similarly, these pathways have been found to be upregulated in human CLAD. Tocilizumab (TCZ), a humanized monoclonal antibody targets the IL-6 receptor subunit alpha and prevents binding of IL-6. We herein report our preliminary experience with adjunctive TCZ therapy for human CLAD.

Methods: We retrospectively reviewed our initial experience with TCZ given after other immunotherapies for CLAD. Linear Regression Slopes for Forced Expiratory Volume-1 sec (FEV-1/Month) (L/month), infection incidence, Single Antigen Flow Cytometry HLA Class I & II Donor-specific antibodies (DSA), Non-HLA Auto-antibodies (EC-1 & 2; AT1R) and adverse events.

Results: Nine LT recipients with CLAD Stages: BOS I (N=2), BOS II (N=4), BOS III (N=2), RAS (N=1) who received ≥ 3 months treatment with TCZ (4-8 mg/Kg/month intravenous) in combination with Rabbit ATG (N=5), Rituximab (N=1) and IVIG (N=9) were analyzed. Median FEV-1/Month Slope PRE- therapy was -0.132±0.148 L/month and for POST-era this was -0.012±0.049 (P=0.011). HLA DSA Class I & II decreased in 75% LT recipients while Non-HLA antibodies were unaffected by these therapies. Respiratory viral infection (N=2) and fatal cardiac event (N=1) occurred in this cohort.

Conclusion: Combination Sequential Immune modulation using Tocilizumab for CLAD after LT can ameliorate the Spirometric decline and would be appropriate for further Multi-Center, controlled clinical trials based on our knowledge of allo-immunologic pathobiology and these pilot human data.

Keywords

Tocilizumab; chronic lung allograft dysfunction; lung transplantation

1. Introduction

Lung Transplant (LT) intermediate term clinical outcomes are significantly diminished, due to the proclivity for Chronic Lung Allograft Dysfunction (CLAD) or chronic allograft rejection [1]. The designation of CLAD encompasses two nonexclusive pathophysiologic phenotypes - (1) *Restrictive*-CLAD (RCLAD) or Restrictive Allograft Syndrome (RAS) and (2) *Obstructive*-CLAD (OCLAD) or Bronchiolitis Obliterans Syndrome (BOS) [2]. Currently, there are no described effective therapies for CLAD, although while palliation is achieved in a minority of patients with such strategies enhance immunosuppressant therapies, Extra-Corporeal Photopheresis (ECP), anti-reflex surgical esophageal fundoplication, and Azithromycin; however, consideration for potential re-transplant may represent the only impactful recourse [1, 3-8]. Both early and late development of Donor-specific HLA Allo-antibodies (DSA) increase the propensity for CLAD, while clinical uncertainty remain regarding a theoretical salutary effect of treatment of either HLA DSA or Non-HLA auto-antibodies [9-12]. Severity of CLAD is characterized by Grade 0-3 for BOS (Obstructive-CLAD) or RAS (Restrictive-CLAD) by the % decrement in FEV-1 when compared to the maximally achieved value POST-LT after exclusion of confounding conditions such as acute respiratory infection, acute cellular rejection, antibody-mediated rejection or mechanical bronchial anastomotic complication [2, 13, 14].

Interleukin-17 (IL-17) and TH-17 cells mediate the development of Bronchiolitis Obliterans (BO) in rodent airway and lung allograft transplant models via local elaboration of IL-6; while neutralization of IL-6 mitigates BO with decreased infiltrating allograft TH-17 cells [15-17]. Tocilizumab (TCZ) is a humanized anti-IL-6α Receptor monoclonal antibody, FDA-approved for treatment of conditions such as Rheumatoid Arthritis, Castleman's Disease, Juvenile Rheumatoid Arthritis, Giant Cell Arteritis and chimeric antigen receptor T- Cell therapy-induced Cytokine Release Syndrome. TCZ targets both membrane-bound and soluble IL-6R(α), preventing binding of IL-6 to both IL-6R and signal transducer glycoprotein-130 (GP-130) complex; thereby, effectuating inhibition of downstream classical signaling and trans-signaling cascades involving the JAK-STAT

pathway. TCZ effectively decreases circulating neutrophils, myeloid dendritic cells, peripheral memory B-Lymphocytes, monocytes, and TH-17 cells [18-21]. Conversely, TCZ increases the CD4+/ CD25+/ FOXP3+ T- Regulator (TReg) Lymphocytes [22] that contribute to allograft accommodation and possibly a state of putative tolerance within the allograft. Importantly, allograft stabilization and reduction in HLA DSA has been effectuated with TCZ treatment for Chronic Antibody Mediated Allograft Rejection (cAMR) after renal transplant [23].

Herein, we report our experience with Combination or Sequential strategies with immune modulation, implementing TCZ, for 'Salvage Therapy' in post-LT recipients who are afflicted by CLAD and had failed conventional therapies with High-dosage Immunoglobulin (IVIG) and polyclonal Rabbit anti-Thymocyte globulin (RATG).

2. Methods

This study entailed a retrospective review of the clinical course of LT recipients who had received $\geq$3 months therapy with Monthly administration of intravenous Tocilizumab (Actemra®) (TCZ) (4-8 mg/Kg/month). Analysis of POST-LT individual patient clinical data, appropriately anonymized, had been approved by the Institutional Review Board for Research. Patients may have received polyclonal Rabbit anti-Thymocyte globulin (RATG) (Thymoglobulin®) (3.75-5.25 mg/Kg) or Rituximab (Rituxan®) (350 mg/M2) $\geq$ 3 months prior to initiation of TCZ as adjunctive therapy. All LT recipients with detectable anti-HLA DSA or Non-HLA auto-antibodies, received monthly infusion of High-dosage Immunoglobulin (IVIG) (2 Gm/Kg/Month). Routine office Spirometry assessments were performed for recipients at intervals of 4-6 weeks PRE- and POST-initiation of TCZ adjunctive therapy according to American Thoracic Society standardization[24]. The Slopes for Forced Expiratory Volume-1 sec (FEV-1)/Month were analyzed for the 3-6 month epoch PRE- therapy by Linear Regression and compared to the FEV-1 data points POST-therapy by paired T-test for repeated measures ($p<0.05$). Immunogenetics Laboratory investigations were routinely performed at 3 month intervals POST-LT by Single Antigen Flow Cytometry for HLA Class I & II Allo-antibodies and expressed as Mean Fluorescence Intensity (MFI). Additional Non-HLA auto-antibodies were assessed for both Endothelial Cell antibodies (ECA-1 & 2) and Anti-Angiotensin II Type 1 Receptor (AT-1R). An exploratory Biomarker assessment of Serum IL-6 Levels by Quantitative Multiplex Assay *(ARUP Labs, Inc.)* was obtained prior to initiation of TCZ therapy [Normal: $\leq$ 5 pg/mL)]as a baseline prior to enrollment. Clinical courses of patients were reviewed Adverse (AE) or Serious Adverse Events (SAE) for concurrent reported episodes of infection, malignancy, gastrointestinal, cardiac or neurologic events and mortality.

3. Results

Our LT Cohort encompassed Nine recipients: Combined Bilateral Lung and Liver (N=1), Single Lung (N=4) and Bilateral Lung (N=4) with Median Age 65 (23-75) years and M;F gender distribution 7:2. Median (±SD) Time POST-LT was 28±30.9 (4-102) months (Table 1). Severity of CLAD was Staged as follows: BOS III (N=2), BOS II (N=4), BOS I (N=2), RAS (N=1). Combination / Sequential immune modulation therapies for the Cohort included: Rabbit Thymoglobulin (N=5), Rituximab (N=1), High-dosage Monthly IVIG (N=9) in combination with our standard protocol maintenance triple-drug immunosuppressive regimen including: Tacrolimus + Mycophenolate Mofetil + Prednisone (0.1 mg/Kg/day).

Table 1 Demographics.

Transplant Type	Additional Therapies	CLAD Type / Stage	Age (yrs) / M:F	Time Post-LT(mos)
Lung-Liver (1)	RATG (5)	BOS III (2)	65(23-75)/7:2	28±30.9(4-102)
SLT (4)	Rituximab (1)	BOS II (4)		
BLT (4)	IVIG (9)	BOS I (2) RAS (1)		

The Serum [IL-6] measured values PRE-TCZ therapy are depicted (Figure 1) with a Median of 11.0±16.2 pg/mL [Normal: ≤ 5.0 pg/mL]. A vignette Summary for individual subjects, responses to TCZ, and clinical outcomes is depicted (Table 2). Subject #1, a complex case, was characterized by development of Liver refractory Acute Allograft rejection with detectable auto-antibodies to AT1R concurrent with development of BOS Stage III involving the Lung Allograft. The patient received unsuccessful Sequential treatments with RATG, Plasma Exchange (PLEX), Methyl Prednisolone and High-dosage IVIG; nevertheless, the Total Bilirubin only decreased subsequent to the initiation of adjunctive TCZ therapy (Figure 2) while stabilization of FEV-1 was maintained over the course of the ensuing 18 months while receiving TCZ infusion every 4 weeks with exception of brief discontinuation (6 weeks) concurrent with Parainfluenza Type 4 Bronchiolitis which resolved without sequelae.

In Figure 3, the FEV-1/Month 'trends' are depicted for individual subjects for both PRE- and POST- (TIME=0) epochs for TCZ therapy. The Linearized Median Slopes for FEV-1/Month for individual subjects are reported (Table 3) with a Median for the Cohort, PRE:-0.132±0.148 and POST:-0.012 ± 0.049 L/Month over the course of 12-18 months therapy (P=0.011).

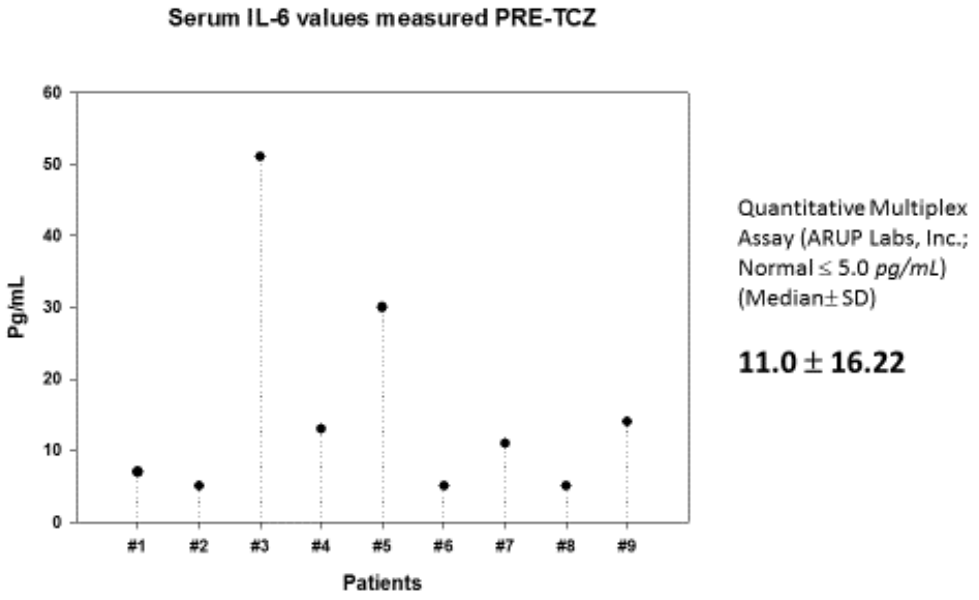

Figure 1 Serum IL-6 concentrations in Serum obtained at baseline prior to treatment with Tocilizumab (anti-IL6Rα) adjunctive therapy for CLAD. No correlation was demonstrated (Pearson Product Moment Correlation = 0.069; P>0.05) for IL-6 values versus FEV-1 L/Month Slope on TCZ therapy however associated with a low Power (0.037) due to reduced sample size.

Table 2 Individual subject clinical courses / vignettes.

#1 - Stable BOS Stage 3 after Combined Bilateral Lung + Orthotopic Liver Transplant and resolved Hyperbilirubinemia associated with concurrent Liver Allograft Acute + Chronic Rejection x 18 months with 18 Monthly doses TCZ.
#2 - Mild progression (-16% decrement) in FEV-1 with BOS Stage 2 with 6 doses TCZ.
#3 - Subject experienced G.I. intolerance with TCZ and received total 3 doses TCZ prior to discontinuation of therapy. Subsequent development of Acute Cellular Rejection (Grade A-3 / B-2) concurrent with recurrent MDR Pseudomonas aeruginosa Bronchopneumonia (Cystic Fibrosis); progression of BOS Stage 1 to BOS Stage 2, transitioned to ECP with FEV-1/Month stability x 3 months.
#4 - Increased FEV-1 (+18%) with 6 months TCZ Therapy; Stable BOS Stage 2.
#5 - Stable BOS Stage 2 x 9 months F/U with total 6 months TCZ therapy; concurrent Stable BK Viremia + Nephropathy.
#6 - Initial Stable BOS Stage 1 x 9 months with 6 months TCZ therapy; complicated by *Metapneumovirus* respiratory bronchiolitis and associated with progression to BOS Stage 2 (-32% decrement FEV-1), hence treated course of RATG + resumed TCZ with subsequent Stable FEV-1 x 6 months.
#7 - Improved RAS (+25% FEV-1) over 9 months F/U with total 3 doses TCZ.
#8 - Stable BOS Stage 2 x 9 months F/U with total 4 doses TCZ complicated presumed 'Sudden Cardiac Death' (no autopsy performed).
#9 - Progressive BOS Stage 3 x 7 months F/U with Total 3 doses TCZ, hence with transition to Palliative Care and patient elected not to pursue program recommended Re-transplantation

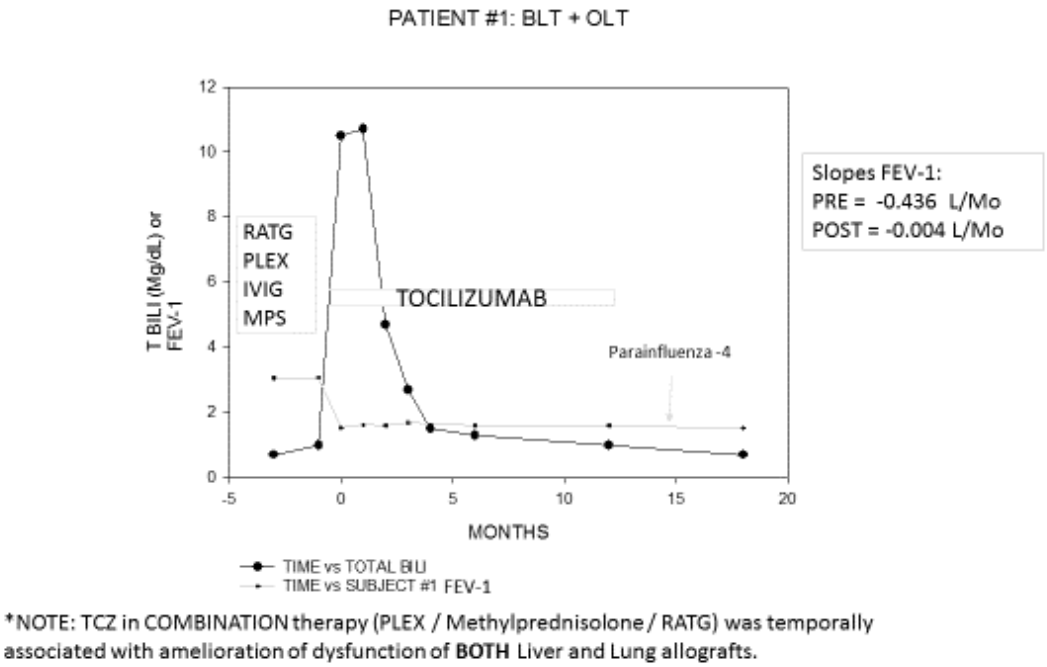

Figure 2 Case Vignette of Subject #1 depicting the therapeutic response associated with Tocilizumab therapy on concurrent Liver Transplant rejection (i.e. Total Bilirubin)[SOLID LINE] and CLAD/BOS Stage 3 (i.e. FEV-1/Month) [DASHED LINE] Stabilization. [RATG= Rabbit Anti-Thymocyte Globulin, PLEX = Plasma Exchange, IVIG = High-dosage Intravenous Immunoglobulin, MPS = Methyl Prednisolone pulsed-therapy].

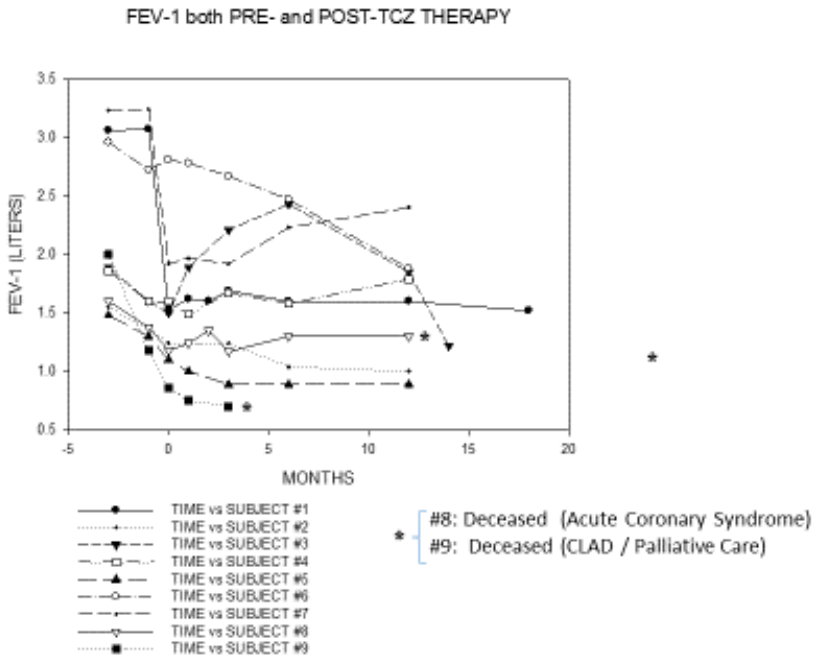

Figure 3 FEV-1/Month Slopes for PRE- and POST-treatment eras for Tocilizumab (T=0). PRE: -0.132±0.148 and POST: -0.012 ±0.049 Liters/Month over the course of 12-18 Months therapy (P=0.011).

Table 3 Median slopes for PRE- and POST-TCZ eras.

SUBJECT	PRE	POST	
1	-0.436	-0.004	
2	-0.101	-0.037	
3	-0.132	-0.012	
4	-0.093	+0.024	
5	-0.121	-0.030	
6	-0.060	-0.113	
7	-0.374	+0.065	
8	-0.136	+0.014	
9	-0.384	+0.040	
Median ± SD	-0.132±0.148	-0.012±0.049*	*P=0.011

The response of HLA Class I & II DSA and Non-HLA auto-antibodies are depicted (Table 4) whereupon Weak/Moderate (MFI < 5000) intensity HLA Class I & II DSA decreased in approximately 75% of subjects while EC-1&2 and AT-1R were unaffected by therapy.

Table 4 HLA Donor-Specific Antibodies (DSA) and NON-HLA Antibodies.

	HLA Class I	HLA Class II	EC-1 & 2	AT-1 Receptor
PRE-	2	6	6	1
POST-	0	2	6	1

HLA DSA MFI were all < 5000

EC-1 & 2 = Anti-Endothelial Cell Ab types 1 & 2

AT-1R= Angiotensin- II Type-1 Receptor Ab

During TCZ therapy, N=2 recipients experienced Community-acquired viral respiratory infection (*Parainfluenza Type 4* and *Human Metapneumovirus*) while N=1 recipient with preexisting *Polyomaviridae* BK Virus Nephropathy (BKVAN) experienced stable BK Viremia and serum Creatinine parameters. One recipient experienced recurrent gastrointestinal adverse effects with TCZ (abdominal pain / diarrheal AE) that required discontinuation after 3 total doses. Mortality occurred in N=2 LT recipients with CLAD, one due to presumed 'Sudden Cardiac Death' and one due to progressive CLAD/BOS-phenotype with chronic respiratory failure after patient decision to transition to Palliative Care.

4. Discussion

To our knowledge, this report constitutes the first described clinical experience with adjunctive inhibition of IL-6 – receptor biology with the implementation of TCZ after the development of CLAD. Post-LT recipients as afflicted by CLAD received treatment with 'Salvage therapies' in an attempt to ameliorate the typical inexorable decrement in Spirometric parameters. Our study suggests that after introduction of TCZ Monthly intravenous therapy, an amelioration in Median

Slope decline for FEV-1/Month (PRE: -0.132± 0.148 and POST: -0.012 ± 0.049 L/Month over the course of 12-18 months of therapy (P=0.011)). Intriguingly, for Subject #1, both FEV-1 demonstrated a maintained stability with BOS Stage III, concurrent with biochemical normalization of severe hyperbilirubinemia, thereby reflecting resolution of liver allograft rejection and dysfunction. LT recipients with CLAD all received concurrent High-dosage (2 Gm/Kg) Monthly IVIG therapy, specifically directed for HLA Class I or II DSA or Non-HLA auto-antibodies in the context of allograft dysfunction. Adjunctive courses of RATG or Rituximab preceded introduction of TCZ by a minimum of three months; suggesting the observed effect on FEV-1/Month Slopes were due to an effect of TCZ on IL-6 – receptor biology. Although not specific for allograft rejection or CLAD, we conducted an exploratory 'Biomarker' assessment of [IL-6] in serum concurrent with initiation of TCZ therapy. The Median IL-6 of 11.0±16.22 pg/mL was increased compared to Normal (≤ 5.0 pg/mL) suggesting IL-6 is associated with the development of CLAD while future investigations should include serial IL-6 mensuration during the course of TCZ therapy. The *Pearson Product Moment Correlation* for the baseline IL-6 serum levels *versus* FEV-1 L/Month Slopes on TCZ therapy was +0.069 (P>0.05) thereby suggesting a "lack of correlation" however the *Power* was only 0.037 due to limited sample size (N=9). Importantly, the effect seen on FEV1 utilizing TCZ in this study suggested that there is more than an association of IL-6 and CLAD and that IL-6 is both biologically active and involved in part, in CLAD pathobiology. Collective data suggests that IL-17 expression stemming from an allo-reactive response interacts with the lung allografts epithelial cells augmenting the secretion of ELR+ CXC chemokines, which are known to contribute to CLAD [25, 26]. More specifically, the ELR+ CXC chemokines expressed from the lung allograft during CLAD can contribute to neutrophil recruitment and angiogenic activity. Additionally, IL-6 is upregulated during CLAD ([27], which then can stimulate the ELR+ CXC chemokine-recruited neutrophils to express additional IL-17, thereby effectuating a 'positive feedback loop' that may ultimately result in vasculopathy and support for the fibroplasia that is characteristic of CLAD. IL-6 also interacts with sIL-6Rα and this complex can engage with GP-130 expressed on endothelial cells via the IL-6 trans signaling pathway [28]. Importantly, IL-6 trans signaling can lead to the upregulation of the angiogenic factors that can induce the vascular remodeling required to support the fibroproliferative process involved in CLAD [25]. Furthermore, IL-6 can cause upregulation of IFNγ from T-Lymphocytes [29]. Importantly, IFNγ then interacts with endothelial cells to express CXCL-11 which has been shown to recruit activated mononuclear cells to the lung allograft and hence, development of allograft lung injury and CLAD [30, 31]. Collectively, these data in combination with our human studies suggest that TCZ is likely inhibiting angiogenesis and CXCL-11 recruitment of allo-reactive mononuclear cells, thus attenuating the processes of CLAD. Moreover, IL-6 down-regulates many of the regulatory cells further allowing for ongoing allograft injury and progressive CLAD and mortality. Our study and the aforementioned potential pathways are corroborated in animal models of CLAD which demonstrated that neutralization of IL-6 reduces graft infiltrating TH-17 cells and mitigates BOS [16, 17].

Previous studies have reported that TH-17 and IL-6 contribute not only to chronic rejection in lung transplant, but also to the chronic rejection of other solid organs [32]. Choi, *et al* reported utility of TCZ as a potential treatment for Chronic Antibody-Mediated Rejection (cAMR) and post-Renal transplant Glomerulopathy in HLA-Sensitized individuals. The TCZ-treated patients demonstrated allograft and patient survival rates of 80% and 91% at 6-years, respectively, with significant reductions in HLA DSA and stabilization of renal function. Importantly, no significant

adverse events (AE) or severe adverse events (SAE) were observed in their cohort of 36 patients treated with TCZ 'Salvage therapy' [23]. Several Open-label Extension (OLE) observational studies of > 2 year duration had confirmed treatment efficacy with TCZ in Rheumatoid arthritis with low immunogenicity with this long term therapy. Safety of TCZ has been supported in nearly a dozen published Phase 3 & 4 Clinical Trials while potential observed SAE reported in Rheumatoid arthritis patients had included: Gastrointestinal perforation, malignancy, myocardial infarction and stroke in an analysis of up to 4.6 years of TCZ exposure [19, 21]. In our study, we observed Community-acquired viral respiratory infection in N=2 recipients and an isolated fatal presumed sudden cardiac event in one patient. The potential contribution of TCZ to these events with background of chronic immunosuppressant treatment, would be difficult to assess from this preliminary experience. A Phase 2, randomized controlled trial of TCZ in N=87 patients with Systemic Sclerosis reported no difference in incidence of SAE while serious infections were more common in the TCZ versus placebo group (16% versus 5%, respectively) [33]; hence, a Phase 3 Trial is currently in progress.

Both early and late development of HLA DSA is associated with increased propensity for CLAD. Further, auto-antibodies to pro-collagen V, AT-1R, K(α)-1 tubulin, vimentin, EC and MICA have been associated with CLAD [11]. In our study, prior assessments by TBBx histopathology had been conducted to exclude alternative etiologies for allograft dysfunction. Immunostaining for C4d+ were *unrevealing* in the assessment for complement deposition and histopathologic evidence for AMR. Presence of HLA Class I or II DSA or Non-HLA auto-antibodies would be classified as "*Possible* Antibody Mediated Rejection" (only 1 of 3 criteria) in the Consensus by *International Society Heart and Lung Transplant* [34]. Regardless, inhibition of IL-6 – receptor biology may indeed have salutary effects for HLA DSA. IL-6 is a predominant cytokine involved in differentiation of B Lymphocytes to IgG-secreting Plasmablasts and then, Plasma cells. Preliminary experience has suggested potential efficacy of TCZ for both 'HLA Desensitization' and treatment of cAMR with Renal transplantation [35, 36]. Our study suggested reduction in HLA Class I and Class II DSA in approximately 75% of subjects during TCZ therapy while no effect on the prevalence of Endothelial cell (EC-1 & 2) nor AT-1R auto-antibodies.

In summary, our data, although limited by the caveats inherent to a retrospective and single center design, represent the first reported clinical experience with IL-6 modulation of CLAD implementing TCZ therapy. The observed effects on both physiologic allograft function and HLA Class I and Class II DSA are consonant with the translational elucidation from rodent models and our understanding of the immunologic pathogenesis of CLAD. Extracorporeal Photopheresis (ECP) has been described to decrease the rate of Spirometric progression of BOS. Morrell, *et al.* had reported reduction in FEV-mL/Month Slopes from -116.0 to -28.9 mL/Month [6]. Mechanisms advanced for an immunologic effect of ECP are myriad, however increase in T-Reg and inflammatory cytokine modulation has been described with decrease in IL-1α and IL-6 [37-39]. Since costly and labor-intensive ECP is currently not yet FDA-approved for treatment of CLAD in the U.S., alternative therapies incorporating TCZ may have potentially similar immunologic basis. We propose that Combination or Sequential 'Salvage therapeutic strategies' for CLAD, incorporating TCZ, would be appropriate for design of multi-center controlled clinical trials.

Author Contributions

David J. Ross, M.D. - Principal Investigator for design and implementation of retrospective study, data analyses and manuscript preparation.

Abbas Ardehali, M.D. - Transplant Surgery; manuscript review.

Christine Natori, R.N. – Clinical Nurse Coordinator; data retrieval.

John A. Belperio, M.D. – Co-Principal Investigator and manuscript preparation.

Competing Interests

The authors have declared that no competing interests exist.

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