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Research Article

Impact of Intravenous Immunoglobulin Replacement Therapy on Hypogammaglobulinemia and Infection in Lung Transplant Recipients

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Abstract

Secondary hypogammaglobulinemia (HGG) from immunosuppression therapy in lung transplant recipients has been associated with increased mortality, morbidity and higher risk of infection. Intravenous immunoglobulin (IVIG) for the treatment of HGG post-lung transplant is not well studied with conflicting evidence regarding efficacy. This single-center, retrospective cohort study analyzed adult lung transplant recipients with HGG receiving ≥1 dose of IVIG 0.3-0.5 g/kg. Resolution of HGG (IgG > 600 mg/dL within 30 days of IVIG) was evaluated for optimal dose and duration of IVIG therapy. Incidence of infection, patient survival, rejection, and chronic lung allograft dysfunction-free survival at 1 year were

compared between resolved and persistent HGG. Results demonstrated majority of patients 46/58 (79.3%) achieved HGG resolution. Severe HGG (IgG < 400 mg/dL) was significantly associated with persistent HGG (50.5% vs 15.2%, p = 0.02), with comparable cumulative IVIG dose and duration between both groups (p = 0.96 and p = 0.39, respectively). No other variables correlated with HGG resolution. Overall infection rates were similar between groups (69.6% vs 58.3%, p = 0.50), suggesting HGG resolution did not correlate with incidence of infection. Lastly, use of IVIG for the treatment of HGG appears to be safe with minimal incidence of thrombosis found within each group.

Keywords
Hypogammaglobulinemia; intravenous immunoglobulin; lung transplantation

1. Introduction

Secondary hypogammaglobulinemia (HGG), a decline in immunoglobulin G (IgG) due to acquired causes of decreased antibody production or increased antibody loss, occurs in ~74% of lung transplant recipients (LTR) at one year post-transplant [1-3]. HGG significantly increases morbidity and mortality and contributes to a heightened risk of infection following lung transplantation [1]. However, there is currently no standardized IgG value to define HGG. Studies suggest the cumulative incidence of mild HGG (IgG < 700 mg/dL) and severe HGG (IgG < 400 mg/dL) to be 58% and 15%, respectively [1, 2]. Pre-transplant chronic obstructive pulmonary disease (COPD) diagnosis, low pre-transplant IgG, and profound immunosuppression, specifically the use of basiliximab and mycophenolate, are known risk factors for HGG in LTR [1, 3]. A higher prevalence of HGG is seen in lung transplantation compared to other solid organ transplants due to the use of more immunosuppression [4, 5]. Severe HGG has been associated with an increased risk of infection, specifically pneumonia, and increased mortality in LTR [6, 7].

Intravenous immunoglobulin (IVIG) replacement therapy for the treatment of HGG and its impact on infection post-lung transplant is not well studied. Current approved, US indications include primary humoral immunodeficiency, chronic immune thrombocytopenic purpura, and chronic inflammatory demyelinating polyneuropathy [8]. With respect to solid organ transplant, its place in therapy is primarily for the treatment of antibody-mediated rejection and BK nephropathy. IVIG is associated with increased risks of thrombosis, acute renal failure, and infusion-related reactions, including hypersensitivity [8]. The incidence of these adverse effects may vary depending on the formulation of IVIG, which differs in osmolarity, pH, and various sugar and immunoglobulin A contents. Additionally, IVIG is considered a high-cost medication with an estimated cost of $4000-$8000 per average dose of 20-40 g (Privigen®) [9].

There is currently conflicting evidence to support the use of IVIG for HGG in LTR in terms of efficacy [10-15]. Additionally, no cumulative dose-comparison studies exist to provide guidance on optimal dose and duration for HGG treatment [1]. The highest level of evidence assessing the efficacy of IVIG for HGG treatment in LTR is a systemic review and meta-analysis of two, single-center, retrospective cohorts [10]. One cohort demonstrated significantly less freedom from chronic allograft dysfunction (CLAD) and lower patient survival in LTR with HGG receiving IVIG, compared to

untreated HGG patients and those without HGG at 2-year post-transplant [11]. The remaining cohort within the analysis concluded mortality to be comparable between LTR with HGG receiving IVIG to those without HGG [12]. Three additional single-center studies found no significant difference in infection, patient survival, CLAD-free survival, or rejection in HGG LTR with and without IVIG replacement therapy [13-15]. Severe HGG was significantly associated with more pneumonia and antibiotic use in one of the prospective studies [14].

In summary, all studies were relatively small, and immunosuppression varied, which may have yielded a differing infection risk at baseline. All studies used different IVIG dosing strategies, including titrating to an IgG level or fixed number of doses and duration. None analyzed HGG resolution and its impact on total incidence of infection. Only one study evaluated safety outcomes [15]. Given the paucity of the data available, the aim of this study is therefore to evaluate the impact of IVIG on HGG resolution and subsequently HGG resolution's impact on infection in LTR. Secondary aims are to characterize safety outcomes and assess for optimal dose and duration of therapy.

2. Materials and Methods

This single-center retrospective cohort was performed on adult (≥18 years) LTR with HGG transplanted between March 2010 to February 2021 at University Health Transplant Institute. The study was approved by the institutional review boards. Eligible patients were identified through an internal database and assessed for inclusion and exclusion criteria. LTR were included if at least one dose of IVIG (Privigen®) 0.3-0.5 g/kg (adjusted body weight) was received for HGG [11-15]. IVIG was administered monthly if given for >1 dose with no dose titration unless patients presented with significant weight change. HGG was defined as IgG < 700 mg/dL. Exclusion criteria included patients with pre-existing common variable immunodeficiency (CVID) and any patient with less than two IgG levels obtained. History of IVIG use for non-HGG indications, HGG prior to transplant, or use of anti-lymphocyte depleting agents within 6 months of IVIG initiation did not lead to exclusion. All LTR received basiliximab for induction immunosuppression per institutional protocol. Patients were divided into two groups for analysis: resolved HGG and persistent HGG post-IVIG therapy.

Incidence of and freedom from infection, patient survival, rejection, and CLAD-free survival at 1 year from IVIG initiation were compared between groups. Other outcomes of interest included the incidence of thrombosis during IVIG therapy, hospitalization due to infection within 6 months of IVIG initiation, and impact of IVIG treatment on donor-specific antibodies (DSA). Additionally, HGG resolution was evaluated for optimal dose and duration of IVIG therapy between groups. Patient demographics, baseline information, and outcomes were collected via electronic health record. Data was collected on the first series of IVIG therapy with multiple series defined as an interim period of > 6 months. IgG levels were collected at time of HGG diagnosis and at 1, 3, 6, 9, and 12 months post-IVIG initiation. DSA during IVIG therapy were measured at the following time points: IVIG initiation ± 30 days, midway through IVIG therapy, and IVIG completion ± 30 days.

2.1 Definition of Outcomes

Resolution of HGG was defined as IgG > 600 mg/dL within 30 days of IVIG completion. Severe HGG included any patient with IgG < 400 mg/dL. Incidence of infection at 6 and 12 months encompassed bacterial, viral, and fungal infections. Bacterial infection was defined as any positive culture resulting in antibiotic treatment. Viral infection consisted of any positive respiratory panel

regardless of symptoms and antiviral treatment, or cytomegalovirus (CMV) viremia/disease, including CMV polymerase chain reaction ≥200 IU/mL. Fungal infection was defined as any positive culture on bronchoalveolar lavage, bronchial washings, or blood resulting in antifungal treatment. Freedom from infection was calculated from start of IVIG therapy. Rejection included biopsy-proven acute cellular, clinical or subclinical antibody-mediated, and mixed as defined by International Society of Heart and Lung Transplant (ISHLT) [16]. Rejection treatment encompassed any administration of high-dose corticosteroids, plasmapheresis, IVIG, or rabbit antithymocyte globulin. Post-transplant CLAD was defined per ISHLT, confirmed via spirometry [17]. Patients with a history of CLAD prior to IVIG administration for HGG were not included in the assessment of CLAD-free survival. Incidence of thrombosis was evaluated for the duration of IVIG therapy through 30-day post-therapy completion.

2.2 Statistical Analysis

Descriptive statistics were used to analyze baseline characteristics. Outcomes were analyzed using chi-squared or two-sided Fisher's exact test, as appropriate. Tests were considered statistically significant with p-value < 0.05. Univariate and multivariate analyses were performed to evaluate impact of variables on HGG resolution. Any variables with p-value < 0.1 on univariate analysis were included in the multivariate analysis with p-value < 0.05 deemed statistically significant. Variables assessed included pre-transplant diagnoses, baseline IgG, immunosuppression at HGG diagnosis, time to HGG diagnosis, history of rejection, severe HGG, and cumulative IVIG dose. JMP16 statistical software was used for data analysis.

3. Results

Out of 488 LTR screened, 68 patients met inclusion criteria and 10 were excluded for having <2 IgG levels obtained, leaving a total of 58 patients. No patients were found to have CVID. Patients were primarily white (65.5%) males (56.9%) with median age of 67.5 [IQR 60-71] years and with either COPD (32.8%) or idiopathic pulmonary fibrosis (27.6%) (Table 1). Median time to HGG diagnosis was 300 [28-1196] days from transplant and median IgG at diagnosis was 497 [426.5-567.5] mg/dL. Thirteen (22.4%) patients presented with severe HGG. Majority of LTR received a bilateral lung transplant (96.5%) and were of moderate (43.1%) or high (43.1%) CMV risk at the time of transplant. Five patients had a history of acute cellular rejection and one patient of antibody-mediated rejection within 6 months of IVIG therapy initiation. Of these patients, one received antilymphocyte-depleting therapy within 6 months of starting IVIG.

Table 1 Baseline Characteristics of Study Population.

Baseline Characteristics, n (%)	Study Population (n = 58)
Male	33 (56.9)
Age, years median [IQR]	67.5 [60-71]
Ethnicity	
White, non-Hispanic	38 (65.5)
Hispanic/Latino	19 (32.8)
Black, non-Hispanic	1 (1.7)

Pre-transplant diagnosis	
Chronic obstructive pulmonary disease	19 (32.8)
Idiopathic pulmonary fibrosis	16 (27.6)
Interstitial lung disease	15 (25.9)
Cystic fibrosis	5 (8.6)
Other	3 (5.1)
Transplant Type	
Bilateral lung	56 (96.5)
Single lung	2 (3.5)
CMV risk at time of transplant	
High (D+/R-)	25 (43.1)
Moderate (R+)	25 (43.1)
Low (D-/R-)	8 (13.8)
Baseline IgG at time of transplant, mg/dL median [IQR]	960.5 [630.3-1106.5]
Time to diagnosis*, days median [IQR]	300 [28-1196]
Immunosuppression at HGG diagnosis	
Tacrolimus trough level, ng/mL median [IQR]	9.1 [6.2-12.1]
MMF dose/day, g median [IQR], (n = 51)	1 [0.5-2.0]
Prednisone dose/day, mg median [IQR], (n = 54)	5 [5-30]
History of rejection†	
Acute cellular	5 (8.6)
Antibody-mediated	2 (3.4)
History of ALA for rejection† (n = 57)	1 (1.8)

ALA = anti-lymphocyte agents; CMV = cytomegalovirus; D = donor, HGG = hypogammaglobulinemia; IQR = interquartile range; MMF = mycophenolate mofetil; R = recipient

*From time of transplant

†Within 6 months of IVIG therapy initiation

Of the included LTR, 46/58 (79.3%) patients achieved HGG resolution (resolved HGG group), while 12/58 (20.1%) did not achieve HGG resolution (persistent HGG group) within 30 days of IVIG therapy completion. Significantly more patients within the persistent HGG group presented with severe HGG at diagnosis (7/46 (15.2%) vs 6/12 (50.0%), p = 0.02). Severe HGG at diagnosis was significant when assessing for variables affecting HGG resolution using univariate analysis. No other variables, including pre-transplant diagnosis and cumulative IVIG dose, correlated with HGG resolution. Statistical significance was lost when analyzing via multivariate analysis. Progression towards HGG resolution among patients of severe and non-severe as well as resolved and persistent HGG at 1, 3, 6, 9, and 12 months post-IVIG initiation is summarized in Figure 1. Median IgG at the time of HGG diagnosis was significantly lower within the persistent HGG group, 511 [449.5-585.5] mg/dL vs 415 [238-526] mg/dL (p = 0.01). Total median cumulative IVIG dose for resolved and persistent HGG were 65 [30-150] g vs 97.5 [23.8-127.5] g, respectively (p = 0.96). Median number of IVIG doses were 2 [1-6] and 4 [1-6] (p = 0.76), respectively. While median duration of therapy was also similar between groups, 83.5 [1-190.5] days vs 97 [1-232] days (p = 0.39) for resolved and persistent HGG groups, respectively. The decision to stop IVIG therapy was dependent on HGG

resolution, alongside patient-specific factors, such as the recurrence of infection and provider discretion.

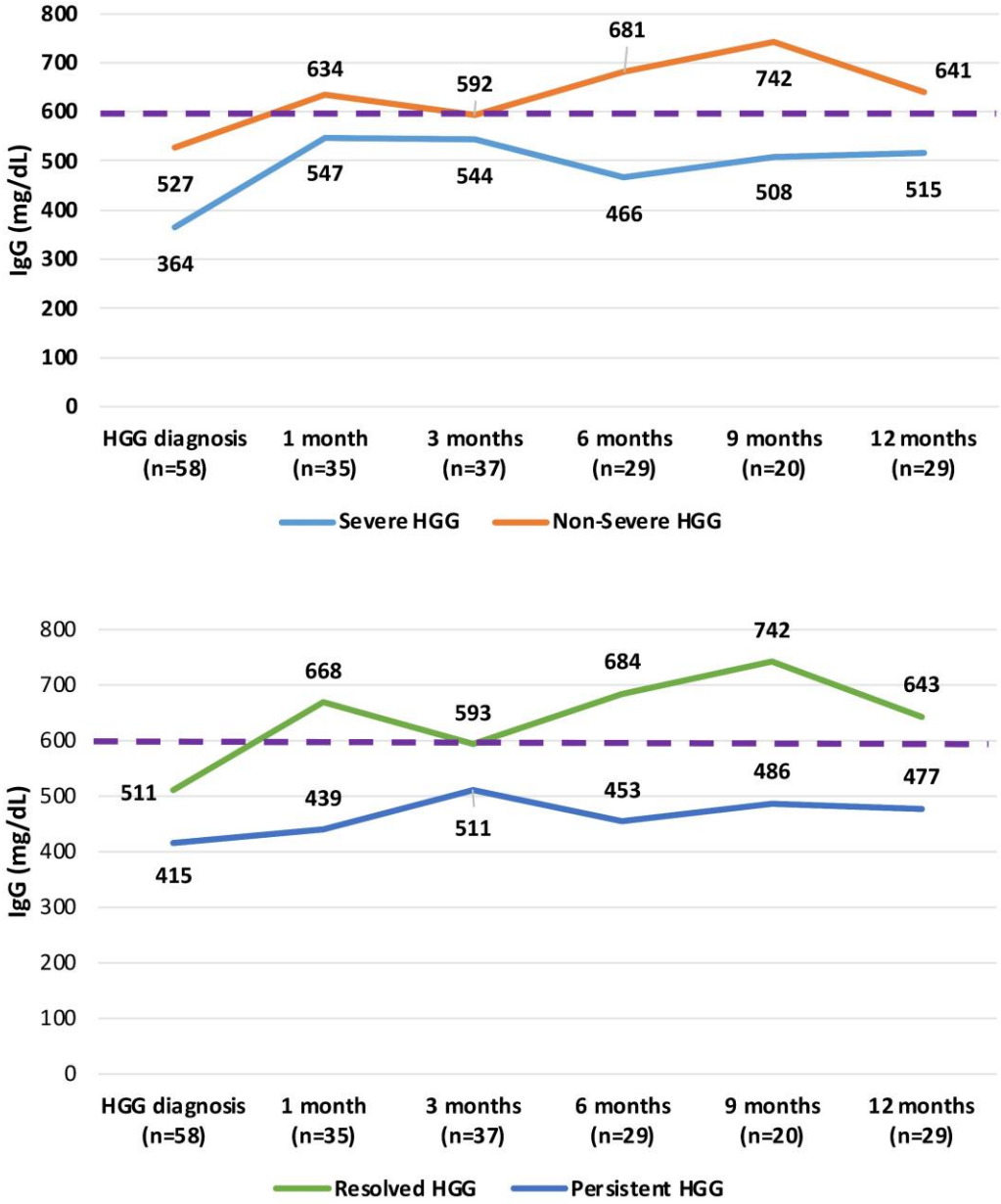

Figure 1 Median IgG Levels from IVIG Initiation.

Total infection rates were similar between resolved and persistent HGG groups within one year post-IVIG initiation, 32/46 (69.6%) vs 7/12 (58.3%) (p = 0.50). Bacterial infections were most common in both groups, followed by viral and fungal infections (Table 2). Most patients had multiple infections within the studied timeframe. Within the resolved HGG group, incidence of bacterial and viral infections was equally seen. Most patients were on antimicrobial prophylaxis at the time of infection, including *Pneumocystis jiroveci* pneumonia (60.3%), CMV (53.4%), and antifungal (51.7%) prophylaxis. Freedom from infection upon starting IVIG therapy was numerically longer for the resolved HGG group, although did not reach statistical significance, median 46.5 [18.3-117.8] days vs 29 [4-184] days (p = 0.76).

Table 2 Incidence of Infection with IVIG Replacement Therapy.

Outcomes, n (%)	Resolved HGG (n = 46)	Persistent HGG (n = 12)	P-value
Any infection[a]	32 (69.6)	7 (58.3)	0.50
Infection at 6 months from IVIG initiation			
Bacterial	15 (32.6)	4 (33.3)	1.00
Viral	11 (23.9)	1 (8.3)	0.43
Fungal	5 (10.9)	2 (16.7)	0.63
Infection at one year from IVIG initiation			
Bacterial	19 (41.3)	6 (50.0)	0.75
Viral	19 (41.3)	2 (16.7)	0.18
Fungal	11 (23.9)	4 (33.3)	0.49
Freedom from infection, days median [IQR]	46.5 [18.3-117.8]	29 [4-183]	0.76
Hospitalization due to infection[b]	17 (37.0)	4 (33.3)	1.00

HGG = hypogammaglobulinemia; IQR = interquartile range; IVIG intravenous immunoglobulin

[a]Within one year post-IVIG initiation

[b]Within 6 months post-IVIG initiation

Patient survival at one year from IVIG therapy initiation was numerically higher for the resolved HGG group, 42/46 (91.3%) vs 9/12 (75.0%), but not statistically significant (p = 0.15) (Table 3). Cause of death within both groups were all related to respiratory failure. Three deaths, one within the resolved HGG group and two within persistent HGG group, were secondary to infection but unclear as to whether this was the primary cause of respiratory failure. A total of 9 patients (19.6%) experienced rejection within the resolved HGG group at one year post-IVIG initiation: 5/46 (10.9%) of acute cellular, 2/46 (4.3%) of antibody-mediated, and 2/46 (4.3%) of mixed or chronic rejection. Although no patients experienced rejection within the persistent HGG group, it was not found to be statistically significant (p = 0.18). Of these, two patients had a history of rejection prior to IVIG initiation. For the treatment of rejection, 7 patients received steroids, two received plasmapheresis plus IVIG, and two received rabbit antithymocyte globulin. Numerically, CLAD-free survival at one year post-IVIG initiation was similar between resolved and persistent HGG groups, 24/31 (77.4%) vs 10/12 (83.3%) (p = 1.00), respectively. Several patients 15/46 (32.6%) within the resolved HGG group were found to have a history of CLAD prior to starting IVIG therapy and were therefore excluded from this outcome.

Table 3 Clinical Outcomes at One Year from IVIG Initiation.

Outcomes, n (%)	Resolved HGG (n = 46)	Persistent HGG (n = 12)	P-value
Patient survival	42 (91.3)	9 (75.0)	0.15
Cause of death			
Respiratory failure	4 (6.5)	3 (25.0)	-
Infection-related	1 (2.2)	2 (16.7)	-
Rejection			

Acute cellular	5 (10.9)	0 (0.0)	-
Antibody-mediated	2 (4.3)	0 (0.0)	-
Fungal	2 (4.3)	0 (0.0)	-
Rejection treatment			
Methylprednisolone ± taper	4 (8.7)	-	-
Plasmapheresis + IVIG	2 (4.3)	-	-
Rabbit antithymocyte globulin	2 (4.3)	-	-
Prednisone taper	3 (6.5)	-	-
CLAD-free survival	24/31 (52.2)	10 (83.3)	1.00

CLAD = chronic lung allograft dysfunction; HGG = hypogammaglobulinemia; IVIG = intravenous immunoglobulin

Thrombosis occurred in four patients while on IVIG therapy. One resolved HGG patient had a non-occlusive thrombus prior to IVIG initiation that developed into a deep vein thrombosis (DVT) after starting therapy. Two additional patients within the resolved HGG group presented with non-occlusive DVT upon receiving IVIG. While one persistent HGG patient developed a non-occlusive thrombus post-IVIG initiation, which resulted in DVT. An estimated one-third of patients were hospitalized due to infection within both groups, 17/46 (37.0%) vs 4/12 (33.3%) ($p = 1.00$). Additionally, de novo DSA was assessed at the start, during, and completion of IVIG therapy for all LTR with HGG. Overall rates were low and did not differ between groups. In the persistent HGG group, one patient (8.3%) developed Class II DSA between IVIG midpoint and therapy completion. Several patients 6/46 (13.0%) within the resolved HGG group had DSA at the time of IVIG initiation and throughout therapy. Of these, five presented with Class II DSA, and one patient had both Class I and II. Three of these patients developed rejection: one of acute cellular, one of antibody-mediated, and one of mixed. Upon completion of IVIG therapy, one patient was found to have resolution of DSA.

4. Discussion

To our knowledge, no other studies have analyzed the efficacy of IVIG for the treatment of HGG with respect to HGG resolution. In this single-center, retrospective cohort, IVIG for the treatment of HGG in LTR achieved HGG resolution in majority of patients (79.3%). Through univariate analysis, patients with severe HGG were significantly less likely to achieve HGG resolution and presented with significantly lower IgG at diagnosis. This is the first study to demonstrate low IgG at diagnosis to impact HGG resolution. Of note, patients who presented with an IgG < 700 mg/dL at baseline were included, and by HGG definition in this study, would have been diagnosed and treated for HGG immediate post-transplant. No other variables through univariate analysis, including pre-transplant diagnoses, such as COPD, immunosuppression therapy at diagnosis, history of rejection, and cumulative IVIG dose were identified to correlate with HGG resolution. This study's population at baseline did present with more patients of COPD diagnosis pre-transplant compared to the national lung transplant data [5]. Other notable differences included a much lower history of rejection prior to IVIG therapy and higher Hispanic population given geographical location.

Consistent with previous studies, HGG resolution was not seen to impact the total incidence of infection [11, 13-15]. Approximately half of LTR were on infection prophylaxis at the time of HGG

diagnosis. Freedom from infection was of modest benefit of ~15 days in the resolved HGG group. A major limitation to evaluating this outcome is the study design and potential for confounders. Patient survival was found to be numerically higher within resolved HGG group (91.3% vs 75.0%) but of no significant difference, which is consistent with Claustre et al [13]. With respect to rejection, results of this study similarly align with previous findings of no significant difference regardless of HGG resolution [13, 14]. However, rejection was only found to occur within the resolved HGG group within this study. This may have clinical significance with respect to the use of IVIG for the treatment of HGG. Additionally, this may also be reflective of patients within the resolved HGG group receiving less overall immunosuppression, allowing for resolution of HGG but at an increased risk of rejection. In assessing de novo DSA while receiving IVIG therapy, numerically more but overall few patients (13.0% vs 8.3%) had DSA within the resolved HGG group, all of Class II. Three of these patients were found to have rejection within one year of IVIG initiation, while one patient without any rejection cleared DSA by therapy completion. These results confirm presence of de novo DSA to be correlated with rejection post-lung transplant and remain unchanged between patients with resolved and persistent HGG post-IVIG therapy. One limitation to note is the possibility of falsely elevated Class II DSA from IVIG therapy, which could have confounded these results [18].

To assess the safety of IVIG use in HGG, this study collected the incidence of thrombosis during IVIG therapy. Renal dysfunction and acute renal failure were not collected due to the inability to rule out other causes of impairment, presenting as a study limitation. However, this has not historically been a notable adverse effect of Privigen® due to its less nephrotoxic formulation of sugar-free content and L-proline stabilizer [8]. Two instances of occlusive DVT occurred during IVIG therapy, one within each group. This incidence is much lower compared to the general venous thromboembolism incidence in LTR of 43.8%, which has been associated with lower survival [19]. Other causes of thrombosis during IVIG therapy, such as hypercoagulable conditions, could not be eliminated as a confounder. Thrombosis, in contrast, did not occur as an adverse event in Lederer et al, the only study to have evaluated safety outcomes for the use of IVIG in HGG [15]. Overall, based on previous findings and the results of this study, IVIG appears to be safe for the treatment of HGG in LTR.

A major limitation of this study is its retrospective design and small sample size, which introduced the potential for confounders and Type II error. Attempts to mitigate confounders were addressed by performance of univariate and multivariate analyses. Nonetheless, larger sample sizes in future, prospective, randomized studies are still needed. Additionally, there may have been missing data in patients who received outpatient IVIG administration externally. This was limited by the availability of external healthcare documentation and institutional electronic health record system (EHR). Results of cumulative IVIG dose and duration between resolved and persistent HGG could have therefore been affected. Another limitation in obtaining the cumulative dose was incomplete records of patients' adjusted body weight used to dose IVIG due to a transition in EHR system. Hence, cumulative dose could only be provided in total grams. Additionally, LTR who received IVIG for non-HGG indications prior to HGG diagnosis were not excluded, which may have confounded the efficacy of IVIG in resolving HGG.

5. Conclusions

In conclusion, majority (79.3%) of LTR achieved HGG resolution with IVIG therapy. Severe HGG

at diagnosis was significantly associated with persistent HGG post-IVIG. Total dose and duration of IVIG did not impact HGG resolution, and HGG resolution was not seen to impact the total incidence of infection in LTR with HGG.

Abbreviations

Chronic allograft dysfunction	(CLAD)
Chronic obstructive pulmonary disease	(COPD)
Common variable immunodeficiency disorder	(CVID)
Cytomegalovirus	(CMV)
Donor-specific antibodies	(DSA)
Electronic health record	(EHR)
Hypogammaglobulinemia	(HGG)
Immunoglobulin G	(IgG)
International Society of Heart and Lung Transplant	(ISHLT)
Intravenous immunoglobulin	(IVIG)
Lung transplant recipients	(LTR)

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Author Contributions

All authors contributed equally to the design/development of the study. Dr. Hall and Dr. Vu were responsible for statistical analysis. Dr. Vu conducted data collection as well as drafted and revised the manuscript. All authors participated in the manuscript editing process for journal submission.

Competing Interests

The authors have declared that no competing interests exist.

Data Availability Statement

Data are available on reasonable request due to restrictions of patient-related information per the Health Insurance Potability and Accountability Act (HIPAA). Data of this study include baseline characteristics of patients and all outcomes of interests. Data are available from the University Health Transplant Institute with the restriction of HIPAA and any other institutional review board policies with respect to data sharing.

References

1. Lam I, Gutman I, Feist A, Mariski M. IVIG replacement for hypogammaglobulinemia in lung transplant patients. OBM Transplant. 2017; 1: 002.
2. Florescu DF, Kalil AC, Qiu F, Schmidt CM, Sandkovsky U. What is the impact of hypogammaglobulinemia on the rate of infections and survival in solid organ transplantation?

A meta-analysis. Am J Transplant. 2013; 13: 2601-2610.
3. Otani IM, Lehman HK, Jongco AM, Tsao LR, Azar AE, Tarrant TK, et al. Practical guidance for the diagnosis and management of secondary hypogammaglobulinemia: A Work Group Report of the AAAAI Primary Immunodeficiency and Altered Immune Response Committees. J Allergy Clin Immunol. 2022; 149: 1525-1560.
4. Mrad A, Chakraborty RK. Lung transplant rejection. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2022.
5. Scientific Registry of Transplant Recipients. Homepage [Internet]. Minneapolis, MN: Scientific Registry of Transplant Recipients; [cited date 2023 April 13]. Available from: https://www.srtr.org.
6. Goldfarb NS, Avery RK, Goormastic M, Mehta AC, Schilz R, Smedira N, et al. Hypogammaglobulinemia in lung transplant recipients. Transplantation. 2001; 71: 242-246.
7. Kawut SM, Shah L, Wilt JS, Dwyer E, Maani PA, Daly TM, et al. Risk factors and outcomes of hypogammaglobulinemia after lung transplantation. Transplantation. 2005; 79: 1723-1726.
8. CSL Behring AG. Human immunoglobulin G (Privigen®) intravenous liquid [Package Insert]. Bern, Switzerland: CSL Behring AG; 2022.
9. Lexicomp. Immune globulin (Intravenous, subcutaneous, and intramuscular). Preparations – US pricing [Internet]. Hudson, OH: Lexicomp; 2024. Available from: http://online.lexi.com/.
10. Bourassa-Blanchette S, Patel V, Knoll GA, Hutton B, Fergusson N, Bennett A, et al. Clinical outcomes of polyvalent immunoglobulin use in solid organ transplant recipients: A systematic review and meta-analysis – Part II: Non-kidney transplant. Clin Transplant. 2019; 33: e13625.
11. Lichvar AB, Ensor CR, Zeevi A, Morrell MR, Pilewski JM, Hayanga JA, et al. Detrimental Association of hypogammaglobulinemia with chronic lung allograft dysfunction and death is not mitigated by on-demand immunoglobulin G replacement after lung transplantation. Prog Transplant. 2019; 29: 18-25.
12. Tsuang WM, Finlen-Copeland A, Budev M, Pieper C, Reynolds J, Palmer SM. Supplementation of hypogammaglobulinemia in lung transplant recipients leads to favorable outcomes. J Heart Lung Transplant. 2014; 33: S69.
13. Claustre J, Quétant S, Camara B, France M, Schummer G, Bedouch P, et al. Nonspecific immunoglobulin replacement in lung transplantation recipients with hypogammaglobulinemia: A cohort study taking into account propensity score and immortal time bias. Transplantation. 2015; 99: 444-450.
14. Petrov AA, Traister RS, Crespo MM, Silveira FP, Xie M, Coffey K, et al. A prospective observational study of hypogammaglobulinemia in the first year after lung transplantation. Transplant Direct. 2018; 4: e372.
15. Lederer DJ, Philip N, Rybak D, Arcasoy SM, Kawut SM. Intravenous immunoglobulin for hypogammaglobulinemia after lung transplantation: A randomized crossover trial. PLoS One. 2014; 9: e103908.
16. Levine DJ, Glanville AR, Aboyoun C, Belperio J, Benden C, Berry GJ, et al. Antibody-mediated rejection of the lung: A consensus report of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2016; 35: 397-406.
17. Verleden GM, Glanville AR, Lease ED, Fisher AJ, Calabrese F, Corris PA, et al. Chronic lung allograft dysfunction: Definition, diagnostic criteria, and approaches to treatment—A consensus report from the Pulmonary Council of the ISHLT. J Heart Lung Transplant. 2019; 38:

493-503.

18. Takamatsu H, Yamada S, Tsuji N, Nakagawa N, Matsuura E, Kasada A, et al. Detection of antibodies against human leukocyte antigen class II in the sera of patients receiving intravenous immunoglobulin. Transplant Direct. 2021; 7: e697.
19. Neto ML, Budev M, Culver DA, Lane CR, Gomes M, Wang XF, et al. Venous thromboembolism after adult lung transplantation: A frequent event associated with lower survival. Transplantation. 2018; 102: 681-687.