Open Access

OBM Transplantation

Review Article

IVIG Replacement for Hypogammaglobulinemia in Lung Transplant Patients

In Lam, Irina Gutman, Ashley Feist, Mark Mariski*

UC San Diego Health, 9300 Campus Point Dr., San Diego, California; E-Mails: inlam@ucsd.edu, igutman@ucsd.edu, aafeist@ucsd.edu, mmariski@ucsd.edu

***Correspondence:** Mark Mariski, PharmD; E-Mail: mmariski@ucsd.edu

Academic Editor: Kamyar Afshar

OBM Transplantation
2017, volume 1, issue 1
doi:10.21926/obm.transplant.1701003

Received: March 10, 2017
Accepted: June 13, 2017
Published: June 22, 2017

Abstract: After lung transplant, infection is a leading contributor to morbidity and mortality, and hypogammaglobulinemia (HGG) may be an important risk factor for many of these infections. Some reports suggest that HGG not only increases the risk of various infections, but also worsens survival. The incidence of HGG has been shown to increase after lung transplant, and may be as high as 70%. In order to mitigate this risk, intravenous immunoglobulin G (IVIG) replacement for the treatment of HGG has been utilized. However, the safety and efficacy of this practice after lung transplant has not been well described. The aim of this article is to review the current literature evaluating the use of IVIG replacement in HGG after lung transplant. In addition, practical considerations of IVIG including administration, adverse effects, and cost will be discussed.

Keywords
Solid Organ Transplant; Hypogammaglobulinemia; IVIG; Immunoglobulin G; Lung Transplant

Introduction

Infection risk in lung transplant patients

Lung transplantation is the last therapeutic option for patients with advanced lung disease. Despite improvements in short term survival, infection and rejection remain the leading causes of long term morbidity and mortality. Infection rates in lung transplant patients are higher compared to other solid organs, likely due to higher levels of immunosuppression and the direct exposure of the lung allograft with the environment [1-3].

Hypogammaglobulinemia post-transplant

Hypogammaglobulinemia (HGG) contributes to the net state of immunosuppression in solid organ recipients [4-11]. Among all solid organ transplant recipients, the reported incidence for mild HGG (IgG<700 mg/dL) is 33-54% and severe HGG (IgG<400mg/dL) is 8-37% [12-14]. Several studies described the high prevalence of HGG after lung transplantation, with incidence up to 74% [12]. One study sought to compare IgG levels before and after transplant and demonstrated that that baseline prevalence of mild HGG (IgG 400-699 mg/dL) in patients who eventually undergo lung transplantation is 15% and the cumulative incidence of mild and severe HGG (IgG <400 mg/dL) after transplantation is 58% and 15%, respectively [1]. It also demonstrated that diagnosis of chronic obstructive pulmonary disease (COPD) is the major determinant of pre-transplant IgG level and an independent risk factor of pre-transplant HGG. Additionally, it showed that cumulative incidences of mild and severe HGG were significantly increased after lung transplant, while the use of mycophenolate mofetil (MMF) and lower pre-transplant IgG levels were independent risk factors for lower post-transplant IgG levels. They also concluded that pre-transplant IgG level is a risk factor for severe post-transplant HGG.

HGG and infection risk

Reports of the association of HGG in solid organ transplant (SOT) recipients with infection have been described in the literature since the 1970s [15]. Several studies have concluded that HGG is associated with increased risk of various types of infections in kidney, liver, lung, and heart transplant recipients, and patients with ventricular assist devices [16-23]. Two studies have found an association between HGG level and risk of clostridium difficile associated infections [24, 25].

In regards to HGG and infection risk specific to lung transplant recipients, Goldfarb and colleagues concluded that patients with HGG (IgG <600 mg/dL) were at a higher risk of bacterial (2.96 vs. 0.45 episodes/ year), fungal (60% vs. 0%) and invasive CMV disease (24% vs. 0%). They also described that patients with severe HGG (IgG <400 mg/dL) had poor survival, however, statistical significance of this finding was not published [26]. In a smaller cohort, Kawut and colleagues found that severe HGG (IgG <400 mg/dL) was associated with higher incidence of pneumonia (63% vs. 16%) and worse survival but did not detect significant association with CMV disease and fungal infections compared to patients with mild or no HGG [13].

In contrast, there are several studies that failed to show an association between HGG and increased risk of infections [14, 27-29]. One study failed to show HGG increases risk of community-

acquired respiratory viral infection in lung transplant patients, and two studies showed no association of infection with HGG early post-operation in kidney transplant recipients [14, 27, 29]. A small study published by Ohsumi and colleagues failed to show an association between HGG and infection but observed a decreased survival in HGG patients [28].

HGG and rejection risk

Another proposed consequence of HGG may be an increased risk of acute and chronic rejection. Yamani and colleagues were amongst the first group to analyze the relationship between HGG on infection and rejection [22]. They concluded that heart transplant recipients with severe HGG (IgG <350 mg/dL) are at a significantly higher risk for opportunistic infections compared to patients with no HGG or mild to moderate HGG (IgG 350-700 mg/dL). In addition, they concluded that three or more rejection episodes and treatment with pulse steroid therapy are associated with severe HGG.

Chambers and colleagues investigated the association between HGG (IgG <700 mg/dL) and bronchiolitis obliterans syndrome (BOS) and found an association between low IgG and shorter BOS-free survival [19].

Discussion

IgG replacement in lung transplant recipient in HGG

Although the association between HGG and infection is well described, evidence of intravenous immunoglobulin G (IVIG) replacement for the treatment of HGG to prevent infection is scarce. Several studies evaluated the potential benefits of IVIG replacement in HGG in heart transplant recipients in the early 2000s [30-34]. Table 1 summarizes the existing literature for IVIG replacement in HGG.

Lederer and colleagues were among the first investigators to evaluate the benefit of IVIG replacement in HGG patients after lung transplant [35]. The study was a randomized, double-blind, placebo-controlled two-period crossover study. The research group recruited 10 patients who were at least 3 months from their lung transplant with IgG level < 500 to participate in the study. Each patient went through two treatment periods. They were randomized to either placebo or IVIG replacement for 12 weeks, patients underwent a twelve weeks washout period, then followed by crossover treatment for 12 weeks. Median time from transplant to enrollment was 187 days (range 119-1330). The primary endpoint of the study was the number of bacterial infections during the treatment period. The authors concluded that treatment with IVIG did not reduce risk of bacterial infections but there was a trend towards increased risk of any infection (OR 2.7; 95%CI 0.95 to 7.6; p=0.06) in placebo group. There were several limitations to this study. This study potentially lacked power to detect differences based on the small sample size and low event rate. Perhaps the most significant limitation was the uncertainty whether there was a carryover effect in patients who had received IVIG first.

The only other study in lung transplant recipients was a single-center, retrospective, observational study that evaluated the effects of IgG replacement with IVIG in patients with HGG [36]. Fifty-four patients with moderate HGG (IgG < 600 mg/dL) who received IVIG replacement

therapy were identified, and they were compared to 30 propensity-score matched control patients with normal serum IgG level. The primary endpoint for this study was survival and chronic lung allograft dysfunction (CLAD)- free survival. Median time to first replacement dose was 3.5 months (IQR 0.5-9.4) and lasted 4.5 months (IQR 1-17.7). The investigators found no difference in survival, CLAD-free survival, rejection or infection rates, suggesting that infection risk is normalized after IgG is replaced in transplant recipients suffering from HGG. Although the results seem promising, there are several limitations to this study. The retrospective nature of this study introduces selection bias. It could be underpowered to detect a difference due to the small sample size. In addition, the study spanned across more than a decade, and therapeutic advances and changes in practice patterns should be considered. It may be reasonable to make the association that repleting with IVIG normalized risk for infection, as previous studies have shown strong association between HGG and infection. The null findings for median survival and CLAD-free survival should be interpreted with careful considerations.

Further large prospective trials should be conducted to strengthen the data for IVIG replacement and reduction of infection, and to uncover its effects on rejection and survival. Future studies should stratify benefits of IVIG therapy based on IgG level (i.e. mild, moderate and severe HGG).

Practical Considerations.

The benefits of replacement must be weighed against the potential rare adverse effects of IVIG such as renal failure, thrombotic events, infusion related reactions and transfusion related acute lung injury (TRALI) [37, 38]. Different formulations of IVIG are available and providers should select the most appropriate product based on the clinical situation and formulary preferences. Gamunex-C® is our preferred inpatient IVIG product at this time. At our outpatient infusion center, we carry four different formulations, Gamunex-C®, Gammagard®, Flebogamma® and Carimune®. We pre-medicate our patients with acetaminophen and diphenhydramine. IVIG infusion is then started at a rate of 1mg/kg/min and rate is doubled every 30 minutes up to a maximum rate of 8 mg/kg/min. Table 2 summarize our approach to managing infusion related reactions. If patients do not tolerate the infusion despite lower infusion rate or altering the pre-medication regimen, we would consider rechallenging with a different formulation depending on patient specific factors and the severity of the infusion related reaction.

Acute Renal Failure and IVIG

Acute renal failure (ARF) is one of the major concerns with the use of IVIG. It is caused by the different stabilizers used in the different formulations of IVIG to prevent dimer and polymer formation. There are two main types of stabilizers, glucose-based and amino acid-based. Glucose-based stabilizers include sucrose (Carimune®), glucose (Gammagard®), maltose (Octagam®), and sorbitol (Flebogamma® and Gammaplex®). Amino acid-based stabilizers include glycine (Gamunex-C® and Gammagard®) and L-proline (Privigen®). Sucrose-based IVIG poses the highest risk of ARF, compared to glucose, maltose and sorbital based products. Amino acid-based products have the lowest risk of ARF but is reported secondary to hemolysis [39]. Patient specific

factors should be considered when selecting IVIG products and renal function should be monitored.

Cost

The high cost of IVIG (~$100-170/g for various IV formulations and more than $200/g for subcutaneous formulation) must be considered against the proposed benefits when this therapy is initiated (i.e. patient quality of life and potential cost savings for infection management and hospital stay). Pharmacoeconomic analysis need to be performed to address cost-effectiveness, since IVIG replacement can be cost prohibitive. When utilizing IVIG in the out-patient population, approval by the insurance through a prior authorization process can be time consuming as HGG is considered "off-label". Providers should be prepared to submit supporting primary literature during for appeals.

Table 1. Published literature on the effects of IVIG replacement in adult solid organ transplant recipients with HGG

Study	Design	Number of subjects (N)	Allograft	HGG cutoff (mg/dL)	IVIG dose	Time to treatment	Type of IgG administered	Results
Carbone, 2012[26]	Retrospective, Controlled	110	Heart	IgG < 600	0.3-0.4 g/kg every 2-3 weeks for at least 3 doses	2.47 months (mean, 1-10 months)	Flebogamma®	Overall mean number of severe infections Before IVIG: 1.95 ± 1.19 After IVIG: 0.33 ± 0.76 P < 0.001
Yamani, 2005[27]	Prospective, randomized, double-blinded, placebo-controlled	23 n= 10 placebo n=13 treatment	Heart	Pre-emptive use of CMVIg, repeat dose if IgG <500	150 mg/kg, IgG level repeat every 4 weeks	111 days (mean, 30-192 days)	Cytogam®	Reduction in CMV infection favoring pre-emptive CMVig, 15.4% vs. 60%; p=0.039
Carbone, 2007[28]	Retrospective	123 n=29 IVIG n=94 no IVIG	Heart	IgG < 600	0.4 g/kg every 21 days until IgG >700 mg/dL	Not reported	Flebogamma®	Decreased risk of death in IVIG group, OR = 0.204; 95% CI 0.04 to 0.92, p=0.03
Yamani, 2001[29]	Prospective, historical control	220 n=111 historical control n=109 pre-emptive IVIG	Heart	IgG < 350	150 mg/kg until level IgG > 350 mg/dL, unknown frequency	Not reported	Cytogam®	Fewer opportunistic infections in IVIG group, 11% vs. 64%, p=0.03 Fewer episodes of grade 2 or higher rejection, 2.5 vs. 4.2 episodes, p = 0.04
Sarmiento, 2005[30]	Case series	N=5	Heart, with rejection and relapsing CMV disease	IgG < 400	0.2-0.4 g/kg every 21 days to maintain IgG level >700 mg/dL	Not reported	Flebogamma®	Control of relapsing CMV disease, free of GI symptoms and absence of CMV antigens in observed patients
Lederer, 2014[32]	Prospective, randomized, double-blinded, placebo-controlled, crossover	11	Lung	IgG < 500	0.4 g/kg every 4 weeks for 12 weeks	187 days (median, range 119-1130)	Gamunex®	Failed to demonstrate benefit
Claustre, 2015[33]	Retrospective	119	Lung	IgG < 600	0.4 g/kg/month until two consecutive IgG> 700 mg/dL	3.5 months (median, IQR 0.5-9.4)	Tegeline before 2009; Clairyg after 2009	No difference in infection rate between substituted group (with HGG) and non-substituted group (without HGG), 2.8 vs. 2.2, p=0.74

Table 2. Management of infusion-related reactions

Infusion-related reactions	**Management**
Rigors	Meperidine 12.5 – 25 mg IV
Hypotension	Hydrocortisone 100 mg IV
Anaphylaxis	Epinephrine 0.3 mg IM Diphenhydramine 25 mg IV Famotidine 20 mg IV

Headache	Decrease infusion rate
Wheezing	Nebulized albuterol

Conclusion

Lung transplant recipients carry the highest risks of infection among all the solid organ transplant patients, especially within the first year post-transplant when level of immunosuppression is often highest [12]. HGG is defined as serum IgG < 700 mg/dL and is observed frequently in lung transplant patients. HGG, especially severe HGG (IgG < 400 mg/dL) has been associated with increased risks of infection, mortality, and rejection. IVIG replacement with non-specific IVIG or CMV-Ig may have some positive effects on infection, although its effects on mortality and rejection are conflicting and requires further elucidation. Based on the existing data, routine IgG level monitoring is reasonable before and after lung transplant. Replacement with IVIG should be considered, especially in patients with severe HGG (IgG < 400 mg/dL) and native and/or donor infections. The benefits of replacement must be weighed against the potential adverse effects and cost of IVIG. Further larger, prospective studies are needed to determine the effects of IVIG replacement on infection, rejection, and mortality.

Acknowledgments

We would like to acknowledge Stefanie Houseknecht, PharmD, for providing her expertise relating to outpatient IVIG infusion and providing information regarding management of adverse effects at our infusion center.

Author Contributions

All authors contributed extensively to the work presented in this paper.

Funding

The authors have no support or funding to report.

Competing Interests

The authors have declared that no competing interests exist.

References

1. Yip NH, Lederer DJ, Kawut SM, Wilt JS, D'Ovidio F, Wang YJ, et al. Immunoglobulin G levels before and after lung transplantation. Am J Respir Crit Care Med. 2006;173:917-921.
2. Yusen R, Edwards L, Dipchand A. The Registry of the International Society for Heart and Lung Transplantation: Thirty-third Adult Lung and Heart–Lung Transplant Report—2016. J Hear Lung Transpl. 2016;35:170-1184.
3. Bando K, Paradis I, Komatsu K. Ananlysis of time-dependent risks for infection, rejection, and death after pulmonary transplantation. J thorac Cardiovasc Surg. 1995;109:49.

4. Corales R, Chua J, Mawhorter S, Young JB, Starling R, Tomford JW, et al. Significant post-transplant hypogammaglobulinemia in six heart transplant recipients: an emerging clinical phenomenon? Transpl Infect Dis. 2000;2:133-139.
5. Avery R, Mawhorter S, Starling R. Hypogammaglobulinemia in Heart Transplant Recipients Treated with Tacrolimus, Mycophenolate, and Prednisone. In: Chicago: 18th Annual Meeting, American Society of Transplantation; 1999:Abstract 355.
6. Smolin M, Rickman W, Hasbargen J. Hypogammaglobulinemia in a renal transplant recipient with antiglomerular basement membrane disease. Am J Kidney Dis. 1988;11:267.
7. Pollock C, Mahony J, Ibels L. Immunoglobulin abnormalities in renal transplant recipient. Transplantation. 1989;47:952.
8. Hogan M, Wilson N, Mutant D. Renal transplantation in a patient with common variable immunodeficiency. Am J Kidney Dis. 1999;33:E7.
9. Van Thiel DH, Finkel R, Friedlander L, Gavaler JS, Wright HI, Gordon R. The association of IgA deficiency but not IgG or IgM deficiency with a reduced patient and graft survival following liver transplantation. Transplantation. 1992;54:269-273.
10. Braun W, Avery R, Gifford RJ, Straffon R. Life after 20 years with kidney transplant: redefined disease profiles and an emerging non diabetic vasculopathy. Transpl Proc. 1997;29:247.
11. Florescu DF. Solid organ transplantation: Hypogammaglobulinaemia and infectious complications after solid organ transplantation. Clin Exp Immunol. 2014;178:54-56.
12. 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.
13. 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.
14. Noell BC, Dawson KL, Seethamraju H. Effect of hypogammaglobulinemia on the incidence of community-acquired respiratory viral infections after lung transplantation. Transplant Proc. 2013;45:2371-2374.
15. Zagornik J, Schmidt P, Kopsa H, Fill W, Deutsch E. Septic candidasis with intrahepatic cholestasis and immunoglobuline deficiency after renal transplantation. Acta hepatogastroenterol. 1975;22:304-309.
16. Fernandez-Ruiz M, Lopez-Medrano F, Varela-Pena P, Lora-Pablos D , García-Reyne A , González E, et al. Monitoring of Immunoglobulin Levels Identifies Kidney Transplant Recipients at High Risk of Infection. Am J Transpl. 2012:2763-2773.
17. Broeders EN, Wissing KM, Hazzan M, Ghisdal L, Hoang AD, Noel C, et al. Evolution of immunoglobulin and mannose binding protein levels after renal transplantation: Association with infectious complications. Transpl Int. 2008;21:57-64.
18. Yamani MH, Chuang HH, Ozduran V, Avery RK, Mawhorter SD, Cook DJ, et al. The impact of hypogammaglobulinemia on infection outcome in patients undergoing ventricular assist device implantation. J Heart Lung Transplant. 2006;25:820-824.
19. Chambers DC, Davies B, Mathews A, Yerkovich ST, Hopkins PM. Bronchiolitis obliterans syndrome, hypogammaglobulinemia, and infectious complications of lung transplantation. J

Hear Lung Transplant. 2013;32:36-43.
20. Gregg KS, Barin B, Pitrak D, Ramaprasad C, Pursell K. Acquired hypogammaglobulinemia in HIV-positive subjects after liver transplantation. Transpl Infect Dis. 2013;15:581-587.
21. Yoshizumi T, Shirabe K, Ikegami T, Yamashita N, Mano Y, Yoshiya S, et al. Decreased immunoglobulin G levels after living-donor liver transplantation is a risk factor for bacterial infection and sepsis. Transpl Infect Dis. 2014;16:225-231.
22. Yamani MH, Avery RK, Mawhorter SD, Young JB, Ratliff NB, Hobbs RE, et al. Hypogammaglobulinemia following cardiac transplantation: A link between rejection and infection. J Hear Lung Transplant. 2001;20:425-430.
23. Sarmiento E, Lanio N, Gallego A, Rodriguez-Molina J, Navarro J, Fernandez-Yañez J, et al. Immune monitoring of anti cytomegalovirus antibodies and risk of cytomegalovirus disease in heart transplantation. Int Immunopharmacol. 2009;9:649-652.
24. Munoz P, Giannella M, Alcala L, Sarmiento E, Yañez JF, Palomo J, et al. Clostridium difficile-associated diarrhea in heart transplant recipients: is hypogammaglobulinemia the answer? J Hear Lung Transpl. 2007;26:907-914.
25. Origuen J, Fernandez-Ruiz M, Lumbreras C, Orellana MÁ, López-Medrano F, Ruiz-Merlo T, et al. Potential role of post-transplant hypogammaglobulinemia in the risk of Clostridium difficile infection after kidney transplantation: a case-control study. Infection. 2015;43:413-422.
26. Goldfarb NS, Avery RK, Goormastic M, Mehta AC, Schilz R, Smedira N, et al. Hypogammaglobulinemia in lung transplant recipients. Transplantation. 2001;71:242-246.
27. Legris T, Picard C, Moal V, Burtey S, Loundou A, Purgus R, et al. Humoral Immunity after kidney transplantation: Impact of two randomized immunosuppressive protocols. Ann Transplant. 2013;18:622-634.
28. Ohsumi A, Chen F, Yamada T, Sato M, Aoyama A , Bando T, et al. Effect of hypogammaglobulinemia after lung transplantation: A single-institution study. Eur J Cardio-thoracic Surg. 2014;45:61-67.
29. Augusto JF, Garnier AS, Demiselle J, Langs V, Picquet J , Legall R, et al. Hypogammaglobulinemia and risk of severe infection in kidney transplant recipients. Transpl Infect Dis. 2016;18:741-751.
30. Carbone J, Sarmiento E, Del Pozo N, Rodriguez-Molina JJ, Navarro J, Fernandez-Yañez J, et al. Restoration of humoral immunity after intravenous immunoglobulin replacement therapy in heart recipients with post-transplant antibody deficiency and severe infections. Clin Transplant. 2012;26:277-283.
31. Yamani MH, Avery R, Mawhorter SD, Mcneill A, Cook D, Ratliff NB, et al. The impact of CytoGam on cardiac transplant recipients with moderate hypogammaglobulinemia: A randomized single-center study. J Hear Lung Transplant. 2005;24:1766-1769.
32. Carbone J, Sarmiento E, Palomo J, Fernandez-Yañez J, Muñoz P, Bouza E, et al. The Potential Impact of Substitutive Therapy With Intravenous Immunoglobulin on the Outcome of Heart Transplant Recipients With Infections. Transplant Proc. 2007;39:2385-2388.
33. Yamani MH, Avery R, Mawhorter S, Young JB, Mcneill A, Cook DJ, et al. Hypogammaglobulinemia after heart transplantation: impact of pre-emptive use of

immunoglobulin replacement (CytoGam) on infection and rejection outcomes. Transpl Infect Dis. 2001;3 Suppl 2(Cmv):40-43.

34. Sarmiento E, Fernàndez-Yáñez J, Muñoz P, Palomo J, Rodríguezmolina JJ, Bermejo J, et al. Hypogammaglobulinemia after heart transplantation: Use of intravenous immunoglobulin replacement therapy in relapsing CMV disease. Int Immunopharmacol. 2005;5:97-101.
35. Lederer DJ, Philip N, Rybak D, Arcasoy SM, Kawut SM. Intravenous immunoglobulin for hypogammaglobulinemia after lung transplantation: A randomized crossover trial. PLoS One. 2014;9:1-7.
36. 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.
37. Looney RJ, Huggins J. Use of intravenous immunoglobulin G (IVIG). Best Pract Res Clin Haematol. 2006;19:3-25.
38. FDA Safety Communication: New boxed warning for thrombosis related to human immune globulin products. U.S. Food and Drug Administration. https://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm375096.htm. Published 2013. Accessed March 8, 2017.
39. Dantal J. Intravenous Immunoglobulins: In-Depth Review of Excipients and Acute Kidney Injury Risk. Am J Nephrol. 2013;38:275-284.