IgM-enriched immunoglobulin as adjuvant therapy for heart transplant after infection of left ventricular assist devices

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Abstract

Patients undergoing heart transplantation (HTx) with active infection of left ventricular assist devices (LVAD) are at high risk for postoperative infections. Between 2021 and 2022, five (P1–P5) of a total of n = 44 patients underwent HTx in our department while suffering from LVAD infection. Postoperatively, patients received adjuvant IgM-enriched human intravenous immunoglobulin (IGM-IVIG), consisting of 76% IgG, 12% IgM, and 12% IgA as a novel approach to prevent infective complications. While in P1, P2, and P4, LVAD driveline infection was known before HTx; in P3 and P5, abscess of device pocket was found incidentally during HTx. After a single dose of IGM-IVIG, all patients showed adequate rise in serum immunoglobulins. In the postoperative course, no patient developed infective complications. All patients were successfully discharged and in good condition at the last follow-up. Therefore, IGM-IVIG seems to be an effective adjuvant treatment for patients undergoing HTx with LVAD infections.

Keywords IGM-IVIG; Driveline infection; Heart transplantation; Infection; Left ventricular assist device; Immunoglobulin

Introduction

Implantation of left ventricular assist devices (LVAD) as a bridge-to-transplant therapy is a common approach in patients suffering from end-stage heart failure.¹ By now, infections are still frequent device-related adverse events not only limiting the outcome of LVAD therapy itself but also affecting consecutive heart transplantation (HTx).¹,² LVAD infections significantly increase the risk of postoperative infections following HTx.³ As infections in general are one of the main causes for early mortality after HTx, patients with present LVAD infections while undergoing HTx are at additional risk.⁴ Moreover, IgG hypogammaglobulinaemia was recently identified as another independent risk factor for infections in HTx.⁵ As Sarmiento and colleagues reported, prophylactic application of immunoglobulin G may reduce infective complications after HTx.⁶ Novel IgM-enriched human immunoglobulin (IGM-IVIG) consists not only of IgG (76%) but also of 12% IgM and 12% IgA. IGM-IVIG has shown promising results in the therapy of sepsis as well as donor-specific antibody-mediated rejection after heart transplantation by directly addressing pathogens, neutralization of bacterial endotoxins and exotoxins, modulation of complement factors, and regulation of immune cells.⁷,⁸ Therefore, adjuvant application of IGM-IVIG may also facilitate protective anti-infective effects in patients undergoing HTx with present LVAD infection.

In the current case series, we now report our early results of adjuvant IGM-IVIG therapy in HTx patients with infected LVAD.
Case report

Ethical approval

This study followed the principles of the Declaration of Helsinki and the Declaration of Istanbul and was approved by our local University ethics committee. All patients gave their informed consent prior to inclusion.

Case series

Between January 2021 and 2022, a total of $n = 44$ patients underwent HTx in our department. Of those, $n = 5$ patients (P1–P5) suffered from a concomitant infection of a LVAD and were included in the present case series (Figure 1). The reported patients all suffered from either driveline infection (Figure 1A) or abscess of the device pocket (Figure 1B). Table 1 shows the detailed clinical data of the five reported patients.

The first patient (P1), a 68-year-old male, underwent LVAD implantation (HeartWare HVAD™, Medtronic plc, Dublin, Ireland) in October 2019 due to ischaemic cardiomyopathy. Approximately 6 months later, the patient developed driveline infection. In the following, the driveline infection caused a peritoneal perforation and consecutive a perforation of the small intestine. Consequently, the patient underwent several abdominal operations including temporary stoma of the jejunum. After a successful revision of the abdominal infection and stoma reversal, the patient was planned for HTx due to residual driveline infection. Finally, 14 months after the initially LVAD implantation, the patient underwent orthotopic HTx. Piperacillin/tazobactam as well as ciprofloxacin were administered as directed antibiotic therapy. Postoperatively, immunoglobulin concentrations were examined and IGM-IVIG administered. Unfortunately, no immunoglobulin concentrations after IGM-IVIG application were available for this patient. In addition, the patients developed postoperative acute kidney injury with transient haemodialysis. Nevertheless, the patient fully recovered and did not experience infection-related adverse events in the postoperative course of the HTx and was discharged to a rehabilitation centre. One year after HTx, the patient is in good clinical condition without any signs of heart failure (NYHA class I).

The second patient (P2) also suffered from driveline infection, approximately 1 year after LVAD implantation (HeartMate 3™, Abbott Laboratories, Chicago, IL, USA) for ischaemic cardiomyopathy. Besides directed therapy with cefazolin, rifampicin, and meropenem, the patient received adjuvant IGM-IVIG directly after HTx. Afterwards, serum immunoglobulins increased by between 33.1% (IgA) and 75.5% (IgM). The patient developed limb ischaemia due to a local dissection of the right femoral artery correlated to the cannulation site of the heart-lung machine. Therefore, the patient underwent patch reconstruction of femoral artery, thrombectomy, and bilateral fasciotomy. Furthermore, he also underwent temporary renal replacement therapy on the intensive care unit. Fortunately, the patient fully recovered and did not experience any infective complications, neither thoracic, nor driveline-related or limb-related. By now, approximately 9 months after HTx, the patient fully recovered (NYHA I).

Patient 3 (P3), another male patient suffering from end-stage ischaemic cardiomyopathy, underwent HTx about 5 years after LVAD implantation (HeartMate 3™). Although no device-related infection was previously known, intraoperatively abscess of the device pocket was found. Therefore, empiric antibiotic therapy by piperacillin/tazobactam was initiated and adjuvant IGM-IVIG administered. Again, a sufficient rise in serum immunoglobulins was established after single

Figure 1  Schematic illustration of patients with infected left ventricular assist device. Patients 1, 2, and 4 suffered from driveline infection (A). In Patient 3 and 5, concomitant pericardial abscess of the device pocket was found intraoperatively (B).
| Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 |
|-----------|-----------|-----------|-----------|-----------|
| HTx date  | 01/2021   | 06/2021   | 06/2021   | 08/2021   | 01/2022   |
| Age at HTx| 68        | 60        | 65        | 49        | 67        |
| Gender    | male      | male      | male      | male      | male      |
| LVAD support duration | 14 months | 12 months | 65 months | 21 months | 4 months  |
| LVAD infection | Driveline infection (P. aeruginosa) | Driveline infection (S. aureus) | Pericardial abscess | Driveline infection (S. aureus) | Pericardial abscess |
| Date of diagnosis of LVAD infection | 10 months before HTx | 7 days before HTx | Intraoperative | 24 days before HTx | Intraoperative |
| Anti-infective therapy | Piperacillin + Tazobactam Ciprofloxacin | Cefazolin Rifampicin Meropenem | Piperacillin + Tazobactam | Levofoxacin Rifampicin Meropenem |
| Pre-IGM-IVIG IgG, mg/dL | 793 | 619 | 827 | 927 | 777 |
| Post-IGM-IVIG IgG, mg/dL (change in %) | not available | 918 (48.3) | 1060 (28.2) | 1084 (17.7) | 939 (20.8) |
| Pre-IGM-IVIG IgA, mg/dL | 243 | 121 | 252 | 240 | 235 |
| Post-IGM-IVIG IgA, mg/dL (change in %) | Not available | 161 (33.1) | 269 (6.7) | 268 (11.7) | 256 (8.9) |
| Pre-IGM-IVIG IgM, mg/dL | 57 | 53 | 70 | 70 | 108 |
| Post-IGM-IVIG IgM, mg/dL (change in %) | Not available | 93 (75.5) | 70 (32.1) | 77 (10.0) | 121 (12.0) |
| Quantity of IGM-IVIG application | Single dose | Single dose | Single dose | Single dose | Single dose |
| Postoperative maximum Leukocytes, $1 \times 10^9/\mu$L | 15.1 | 21.7 | 28.4 | 18.6 | 28.4 |
| Postoperative minimum Leukocytes, $1 \times 10^9/\mu$L | 5.8 | 5.1 | 5.9 | 4.8 | 5.7 |
| Postoperative maximum CRP, mg/dL | 8.3 | 11.8 | 3.1 | 16.3 | 4.9 |
| Postoperative maximum PCT, ng/mL | 5.95 | 20.10 | 1.53 | 4.05 | 23.00 |
| IGM-IVIG-related adverse events | None | None | None | None | None |
| Postoperative infective complications | None | None | None | None | None |
| Postoperative adverse events | Acute kidney injury requiring haemodialysis on ICU | Limb ischaemia due to dissection of femoral artery | Acute kidney injury requiring haemodialysis on ICU | Sinoatrial block requiring pacemaker implantation | Acute kidney injury requiring haemodialysis on ICU |
| In-hospital outcome | Discharge to rehab centre | Discharge to rehab centre | Discharge to rehab centre | Discharge to rehab centre | Discharge to rehab centre |
| Date of last follow-up | 12 months after HTx | 9 months after HTx | 7 months after HTx | 6 months after HTx | 1 month after HTx |
| Status of last follow-up | Good clinical condition | Good clinical condition | Good clinical condition | Good clinical condition | Good clinical condition, still in rehab centre |

CRP, C-reactive protein; HTx, heart transplantation; ICU, intensive care unit; LVAD, left ventricular assist device; PCT, procalcitonin. Patients were postoperatively treated with adjuvant intravenous IgM-enriched human immunoglobulin (IGM-IVIG). Serum immunoglobulin reference range: IgG = 700–1600 mg/dL; IgA = 70–500 mg/dL; IgM = 40–230 mg/dL.
IGM-IVIG for HTx with Driveline infections

IGM-IVIG application

Appendix 1 shows the detailed study protocol. In brief, laboratory values including IgG, IgA, and IgM concentrations were examined directly after the HTx procedure. Afterwards, IGM-IVIG (Pentaglobin®, Biotest AG, Dreieich, Germany) was applied with a dose of 3.0 mL/kg body weight (equal to 150 mg immunoglobulins/kg body weight) as a continuous venous infusion with a maximum infusion rate of 50 mL/h. Laboratory examinations were repeated the next day and in patients with IgG or IgM concentration below the reference range (IgG = 700–1600 mg/dL; IgM = 40–230 mg/dL) IGM-IVIG application was repeated with a dose of 5.0 mL/kg body weight (equal to 250 mg/kg body weight). Laboratory values of the patients are displayed in Table 1.

Immunosuppression and anti-infective therapy

All patients followed the same immunosuppressive therapy consisting of prednisolone, tacrolimus, and mycophenolate mofetil. No additional induction therapy was applied. In guidance with the microbiologic examinations, besides adjuvant IGM-IVIG, patients were treated with intravenous antibiotics (Table 1).

Discussion

In the current case series, we summarized our first results of the adjuvant treatment of patients undergoing HTx with present infection of a LVAD by IGM-IVIG. By now, we have included five patients, none of them developed postoperative infective complications or therapy-related adverse events.

While P1, P2, and P4 suffered from previously known driveline infection, in P3 and P5, infection of device pocket was found incidentally during the HTx procedure. Both driveline and pocket infection are the most common forms of LVAD infections reported in the literature. Although no bloodstream infection, which is associated with a high risk of morbidity and mortality in LVAD patients, was diagnosed in our case series, all patients were at a high risk for severe postoperative infective complications due to the immunosuppression after HTx. In a cohort study of Swiss VAD patients, one third of patients with LVAD infection developed infective complications after HTx. Furthermore, the study reported 33.3% 1 year mortality for patients undergoing HTx with LVAD infection compared with 0% for patients with non-infected LVAD. Furthermore, in a previously reported study, we observed severe postoperative infective complications (sepsis, pneumonia, and infective wound healing disorders) in 12.3% of patients with pre-transplant LVAD driveline infect who were treated with antibiotics but without IGM-IVIG application. In contrast, after adjuvant IGM-IVIG application, we did not observe any infective complications in our case series, and no death occurred so far. Moreover, despite active LVAD infection, postoperative serum values of C-reactive protein and procalcitonin remained low and were comparable with reported data for HTx patients without infections.

As IgG hypogammaglobulinaemia is a risk factor for infections in HTx patients, Sarmiento and colleagues reported beneficial effects of prophylactic IgG application. However, in contrast to our case series, IgG was only administered in patients with proved postoperative hypogammaglobulinaemia, only one fourth of the reported patients underwent HTx after LVAD implantation and none of them suffered from present infections. In addition, instead of stand-alone intravenous IgG, we applied IGM-IVIG which consists of additional IgM and IgA and has been reported to outclass standard IgG application due to its enhanced anti-infective effects.

As reported, IGM-IVIG application was used as an adjuvant treatment in the current case series. Therefore, adequate antibiotic therapy was of course crucial in all patients. As suggested by the literature, antibiotic regime was selected in guidance with the microbiology and pursued for 7 to 14 days after the HTx in every patient.
Three patients developed transient acute kidney injury with temporary haemodialysis on the intensive care unit. IGM-IVIG application may be related to acute renal failure, especially in patients with already existing chronic renal insufficiency. However, risk of acute renal dysfunction is relatively high in LAVD patients undergoing HTx, and therefore, this was most likely not related to the IGM-IVIG application. Furthermore, observed limb ischaemia of P2 was caused by a local dissection of femoral vessel correlated to the cannulation of the heart-lung machine and successfully treated by vascular surgery. No other potential therapy-related adverse events were observed which was in line with our previous experiences with IGM-IVIG therapy in HTx patients.

Conclusion

Infections are a life-threatening complication after HTx. In particular, patients with LVAD infections or hypogammaglobulinaemia are at high risk for severe postoperative infective complications. After adjuvant application of IGM-IVIG, we did not observe a single case of postoperative infections in this series. Furthermore, we did not experience any therapy-related adverse side effects. Although larger studies are obviously needed to prove these early results, IGM-IVIG application may act as an effective adjuvant therapy in patients undergoing HTx with LVAD infections.

Acknowledgement

Figure 1 was created with Biorender.com. Open Access funding enabled and organized by Projekt DEAL.

Conflict of interest

M.B.I. and U.B. have received travel research grants from Biotest AG, Dreieich, Germany.

References

1. Shah P, Yuzefpolskaya M, Hickey GW, Breathett K, Wever-Pinzon O, Ton VK, Hiesinger W, Koehl D, Kirklin JK, Cantor RS, Jacobs JP, Habib RH, Pagani FD, Goldstein DJ. Twelfth interagency registry for mechanically assisted circulatory support report: Readmissions after left ventricular assist device. Ann Thorac Surg. 2022; 113: 722–737.
2. Immohr MB, Boeken U, Mueller F, Prashovikj E, Morshuis M, Böttger C, Aubin H, Gummert J, Akhyari P, Lichtenberg A, Schramm R. Complications of left ventricular assist devices causing high urgency status on waiting list: Impact on outcome after heart transplantation. ESC Heart Fail. 2021; 8: 1253–1262.
3. Moayedi Y, Multani A, Bunce PE, Henricksen E, Lee R, Yang W, Gomez CA, Garvert DW, Tremblay-Gravel M, Duclos S, Hiesinger W, Ross HJ, Khush KK, Montoya JG, Teuteberg JJ. Outcomes of patients with infection related to a ventricular assist device after heart transplantation. Clin Transplant. 2019; 33: e13692.
4. Chambers DC, Perch M, Zuckermann A, Cherikh WS, Harhay MO, Hayes D Jr, Hisch E, Khush KK, Potena L, Sadavarte A, Lindblad K, Singh TP, Stehlik J, International Society for Heart and Lung Transplantation. The international th-

Funding

The authors did not receive any funding for this study.

Appendix

Study protocol

Inclusion criteria

- Adult heart transplantation
- Active infection of ventricular assist device (left or biventricular assistance)

Laboratory examinations:

- Before IGM-IVIG applications: routine blood count, CRP, PCT, II-6, IgA IgG, IgM
- First day after IGM-IVIG applications: routine blood count, CRP, PCT, II-6, IgA IgG, IgM

Clinical examinations:

- Hemodynamics
- Thoracic X-ray

Intervention:

- 3 mL/kg body weight (= 150 mg) intravenous IGM-IVIG (Pentaglobin®, Biotest AG, Dreieich, Germany) directly after heart transplantation with a maximum infusion rate of 50 mL/h
- Repetition of IGM-IVIG application 5 mL/kg body weight (= 250 mg) per day in patients with IgG or IgM concentration below the reference range (IgG = 700–1600 mg/dL; IgM = 40–230 mg/dL)
reric organ transplant registry of the International Society for Heart and Lung Transplantation: Thirty-eighth adult lung transplantation report - 2021; focus on recipient characteristics. *J Heart Lung Transplant.* 2021; 40: 1060–1072.

5. Sarmiento E, Jaramillo M, Calahorra L, Fernandez-Yañez J, Gomez-Sanchez M, Crespo-Leiro MG, Paniagua M, Almenar L, Cebrian M, Rabago G, Levy B, Segovia J, Gomez-Bueno M, Lopez J, Mirabet S, Navarro J, Rodriguez-Molina JJ, Fernandez-Cruz E, Carbone J. Evaluation of humoral immunity profiles to identify heart recipients at risk for development of severe infections: A multicenter prospective study. *J Heart Lung Transplant.* 2017; 36: 529–539.

6. Sarmiento E, Diez P, Arraya M, Jaramillo M, Calahorra L, Fernandez-Yañez J, Palomo J, Sousa I, Hortal J, Barrio J, Alonso R, Munoz P, Navarro J, Vicario J, Fernandez-Cruz E, Carbone J. Early intravenous immunoglobulin replacement in hypogammaglobulinemic heart transplant recipients: Results of a clinical trial. *Transpl Infect Dis.* 2016; 18: 832–843.

7. Nierhaus A, Berlot G, Kindgen-Milles D, Muller E, Girardis M. Best-practice IgM- and IgA-enriched immunoglobulin use in patients with sepsis. *Ann Intensive Care.* 2020; 10: 132.

8. Immohr MB, Akhyari P, Aubin H, Westenfeld R, Mehdiyan A, Bruno RR, Sipahi NF, Erbel-Khurtsidze S, Reinecke P, Tudorache I, Lichtenberg A, Boeken U. Treatment of donor-specific antibody-mediated rejection after heart transplantation by IgM-enriched human immunoglobulin. *ESC Heart Fail.* 2021; 8: 3413–3417.

9. O’Horo JC, Abu Saleh OM, Stulak JM, Wilhelm MP, Baddour LM, Rizwan Sohail M. Left ventricular assist device infections: A systematic review. *ASAIO J.* 2018; 64: 287–294.

10. Swiss Transplant Cohort Study (STCS), Héquet D, Kraulidis G, Carrel T, Cusini A, Garzoni C, Hullin R, Meylan PR, Mohaci P, Mueller NJ, Ruschitzka F, Tozzi P, van Delden C, Weisser M, Wilhelm MJ, Pascual M, Manuel O. Ventricular assist devices as bridge to heart transplantation: Impact on post-transplant infections. *BMC Infect Dis.* 2016; 16: 321.

11. Franeková J, Sečník P Jr, Lavriková P, Kubíček Z, Hošková L, Kieslichová E, Jabor A. Serial measurement of procalcitonin, and C-reactive protein in the early postoperative period and the response to antithymocyte globulin administration after heart transplantation. *Clin Transplant.* 2017; 31: e12870.

12. Rossmann FS, Kropec A, Laverde D, Saaverda FR, Wobser D, Huebner J. In vitro and in vivo activity of hyperimmune globulin preparations against multiresistant nosocomial pathogens. *Infection.* 2015; 43: 169–175.

13. Stracquadanio S, Lo Verde F, Cialfi A, Zega A, Stefani S, Calif V. Titration of IgG contained in an intravenous IgM-enriched preparation against selected pathogens involved in sepsis. *Immunobiology.* 2020; 225: 151897.

14. Esquer Garrigos Z, Castillo Almeida NE, Gurrum P, Corsini Campioli CG, Stulak JM, Rizza SA, Baddour LM, Rizwan Sohail M, Rizwan Sohail M. Management and Outcome of Left Ventricular Assist Device Infections in Patients Undergoing Cardiac Transplantation. In *Open forum infectious diseases,* Vol. 7; 2020. ofaa303.

15. Tibrewala A, Khush KK, Cherikh WS, Foutz J, Stehlik J, Rich JD. Risk of renal dysfunction following heart transplantation in patients bridged with a left ventricular assist device. *ASAIO J.* 2021; 68: 646–653.