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CASE REPORT

Treatment of donor-specific antibody-mediated rejection after heart transplantation by IgM-enriched human immunoglobulin

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Abstract

Antibody-mediated graft rejection caused by donor-specific antibodies (DSA-MR) remains a serious problem after heart transplantation (HTx). IgM-enriched human intravenous immunoglobulin (IGM-IVIG) consists of 76% IgG, 12% IgM, and 12% IgA and provides a new multifactorial approach for DSA-MR. Between 2017 and 2020, four (P1–4) of 102 patients developed DSA-MR after HTx in our department and were repetitively treated with IGM-IVIG in combination with anti-thymocyte globulin. While in P1 and P4, DSA-MR occurred within the early post-operative interval, P2 and P3 developed DSA-MR approximately 1 year after transplantation. An impairment of ventricular function was observed in three of four patients. Furthermore, P1 and P4 suffered from malign ventricular arrhythmias. After the application of IGM-IVIG, the ventricular function recovered, and all patients could be discharged from the hospital. As part of a multifactorial therapeutic approach, treatment with IGM-IVIG seems to be a safe and effective strategy to address DSA-MR.

Keywords Heart transplantation; Antibody mediated rejection; Immunoglobulin; IgM; Donor specific antibody

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Introduction

Although the incidence of treated graft rejection after heart transplantation (HTx) decreased in the recent years, the 2019 annual report of the International Society for Heart and Lung Transplantation still lists acute organ rejection as one of the main causes for death in transplanted patients.[1] In contrast to cellular rejection, detection and treatment of antibody-mediated rejection (AMR) is still challenging today.[2] Circulating donor-specific antibodies (DSA) against human leucocyte antigen (HLA) can lead to donor-specific antibody-mediated rejection (DSA-MR) and increase post-transplant morbidity and mortality.[3–5] As DSA can bind to the myocardium, severe cases of DSA-MR can sometimes even be observed in patients without the detection of circulating DSA.[4] Despite current developments, therapy of DSA-MR is often inadequate and related to poor outcome.[2,6] In general, therapy of DSA-MR involves a combination of steroids, plasmapheresis, extracorporeal photopheresis, anti-T-lymphocyte IgG, and intravenous immunoglobulin (IVIG) applications.[4,6,7] While common therapeutic IVIG consist of IgG only, novel intravenous IgM-enriched immunoglobulin (IGM-IVIG) consist of a combination of 76% IgG, 12% IgM, and 12% IgA and can address DSA-MR by scavenging activated complement, neutralization of DSA, inhibition of the activation of cytotoxicity effector cells, inhibition of tissue migration granulocytes and monocytes, and activation of regulatory T cells.[8–12] IGM-IVIG are by now regularly used in the therapy of severe sepsis and showed first promising results in the therapy of DSA-MR in lung and heart transplantation.[13–15]

By this case series, we report our results in the treatment of patients suffering from DSA-MR after HTx with a combination therapy containing the usage of IGM-IVIG.

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 2017 and 2020, a total of *n* = 102 patients underwent HTx in our department. Of those, *n* = 4 patients developed DSA-MR and were treated with IGM-IVIG. *Table 1* displays an overview of the clinical and immunological data of the four reported patients (*Table 1*).

The first patient (P1) was transplanted in 2018 after development of persistent driveline infection after more than 2 years of left ventricular assist device (LVAD) support due to dilated cardiomyopathy (DCM). At the sixth post-operative day, the patient suffered from new-onset supraventricular and ventricular arrhythmia with severe impairment of biventricular function. Myocardial biopsy revealed a severe acute AMR (pAMR3) (*Figure 1*). Although there was no direct detection of circulating DSA, this was most likely and therefore therapy was started as a combination of immunoadsorption and anti-T-lymphocyte IgG (Thymoglobuline®, Sanofi-Aventis Deutschland GmbH, Frankfurt, Germany). After two times of immunoadsorption, therapy was amended by IGM-IVIG application. The arrhythmias stopped, and the ventricular function recovered. One week later, histology confirmed regression of rejection in the myocardium (pAMR1). Finally, the patient was discharged from the hospital approximately 1 month after HTx. Recent follow-up examination showed no recurrence of rejection and the patient being in good clinical conditions.

Patient 2 (P2), a 56-year-old female, underwent HTx in 2017 after approximately 2 years of LVAD support because of end-stage heart failure caused by DCM. After HTx, the patient was discharged home in stable conditions. Routine endomyocardial biopsies revealed cellular rejection (ISHLT G2R) about 2 months after the transplantation. Acute rejection was treated with cortisone. Another 2 months later, persistent immunohistological inflammation was still observed in

Table 1 Patient characteristics

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4
HTx date	2018	2017	2017	2020
Age at HTx	30 years	56 years	46 years	68 years
Sex	Male	Female	Male	Male
Previous LVAD	2 years support	2 years support	None	2 years support
Known presence of anti-HLA-antibodies at HTx	None	Anti-HLA class I	Anti-HLA class I & II	Anti-HLA class I
MFI of anti-HLA-antibodies before HTx	None	15,776	599	3,371
Onset auf DSA-MR	6th POD	4 months later	1.5 years later	10th POD
Symptoms	Arrhythmia Biventricular failure	NYHA II-III	None	Arrhythmia Biventricular failure
Biopsy result	pAMR3	negative	pAMR2	negative
Circulating DSA	Not detected	Anti-HLA-B13	Anti-HLA-DQ7, -DQ8, DR53	Not-detected
De-novo DSA	n/a	no	no	no
DSA MFI pre-treatment	n/a	-B13: 5057	-DQ7: 23391 -DQ8: 23639 -DR53:22115 -B38: 1631 -CW12: 2646	n/a
Therapy	Immunabsorption Anti-T-lymphocyte IgG IGM-IVIG	Plasmapheresis IVIG IGM-IVIG	Plasmapheresis Anti-T-lymphocyte IgG IGM-IVIG	va-ECMO Anti-T-lymphocyte IgG IGM-IVIG
DSA MFI post-treatment	n/a	1452	-DQ7: 24465 -DQ8: 23600 -DR53:17950 -B38: 443 -CW12: 864	n/a
Outcome	Full recovery	Full recovery	Full recovery	Full recovery

Overview of the clinical and immunological findings of the four patients.
AMR, antibody-mediated rejection; DSA, donor-specific antibody; DSA-MR, donor-specific antibody-mediated rejection; HLA, human leucocyte antigen; HTx, heart transplantation; LVAD, left ventricular assist device; MFI, mean fluorescence intensity.

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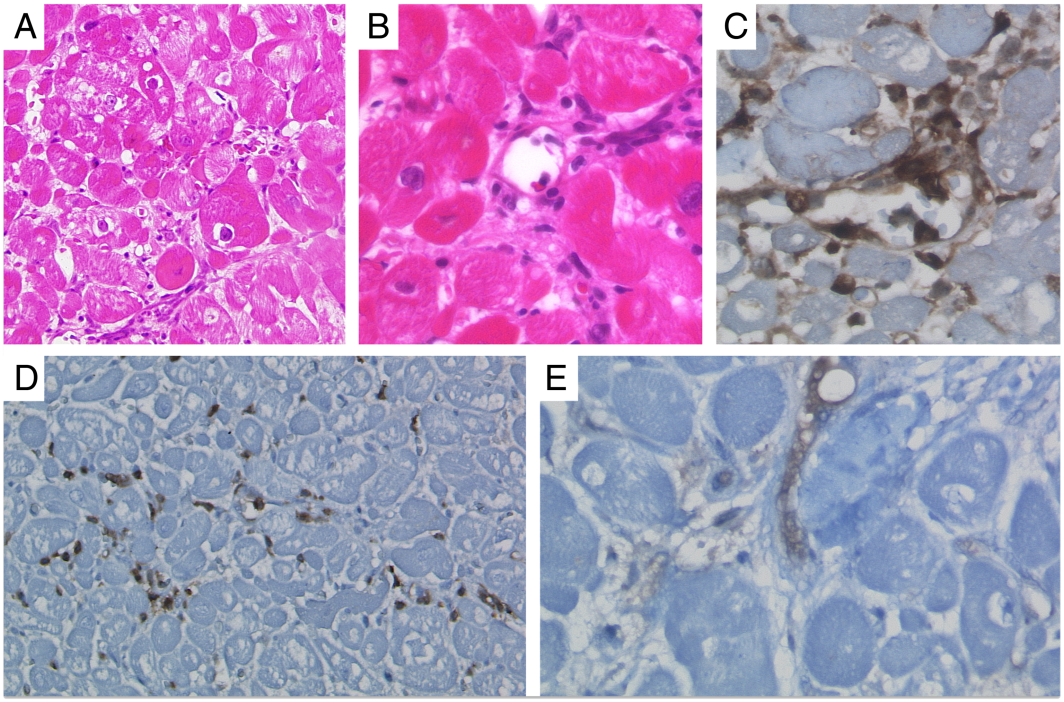
Figure 1 Myocardial biopsy of a patient suffering from new-onset malign arrhythmia displaying interstitial oedema, myocyte necrosis, karyohexis and inflammatory cell infiltrates (A + B); $CD3^+$-lymphocytes, neutrophils, and mast cells (C); intravascular $CD68^+$-macrophages (D); and endothelial C4d-depositions (E) as signs of severe AMR (pAMR3). (A) Haematoxylin, and eosin staining, 20-times magnification; (B) haematoxylin and eosin staining, 40-times magnification; (C) CD3-antibody staining, 20-times magnification; (D) CD68-antibody staining, 40-times magnification; (E) C4d-antibody staining, 40-times magnification. Figure adapted from Sipahi *et al.*[13]



the myocardium, and the patient suffered from minor symptoms of heart failure (New York Heart Association II–III) with a mild impairment of the left ventricular function. Further investigations discovered IgG-antibodies against HLA class 1, PRA 97% with DSA (anti-HLA-B13). In the synopsis of all diagnostic findings and after the exclusion of other potential causes, AMR was most likely in this patient. Therefore, P2 underwent plasmapheresis for five consecutive days as well as antibody treatment with IVIG (Iqymune®, LFB Biomedicaments S.A., Courtaboeuf Cedex, France). DSA titre could be lowered but were still detectable 2 months later. Another 5 days cycle of plasmapheresis was initialized, and the patient treated with IGM-IVIG for 3 days. Afterwards, pathological examinations of the endomyocardium showed only mild cellular rejection (ISHLT G1R) and no humoral rejection (pAMR0). After another treatment with IGM-IVIG, the patient showed no recurrence of DSA-MR by now and was in stable conditions ever since.

The third patient (P3), a male suffering from end-stage DCM, was transplanted in 2017 at the age of 46 years. About one and a half year after the transplantation, the patient was readmitted to the hospital because of severe diarrhoea suspicious of cytomegalovirus colitis. Soon after admission, diarrhoea stopped, and pathological examination of colon biopsies revealed no pathological findings. However, routine biopsies of the right ventricular myocardium of the patient showed acute humoral rejection (pAMR2). Further examinations showed donor specific IgG antibodies against HLA class 1 and 2 (HLA-DQ7, HLA-DQ8, and HLA-DR53). The patient was then treated by a combination of plasmapheresis, human anti-T-lymphocyte IgG and IGM-IVIG. Concomitant hospital acquired pneumonia was treated by meropenem. The cardiac function was good without any signs of impaired graft function. Two weeks later, control biopsies and cardiac magnetic resonance imaging found no evidence for persistent rejection, and the patient was successfully discharged home in good clinical conditions.

The fourth patient (P4), a male suffering from severe device-related neurological complications after LVAD implantation because of ischemic cardiomyopathy, was transplanted in 2020 at the age of 68 years. Ten days later, the patient developed refractory malign arrhythmia with need for cardiopulmonary resuscitation and implantation of veno-arterial membrane oxygenation (va-ECMO). Recent myocardial biopsies did not show signs of acute rejection or other potential causes of acute allograft dysfunction. Therefore, we treated the patient with anti-T-lymphocyte IgG and IGM-IVIG because of presence of DSA. In the following, the patient was stabilized and va-ECMO could be successfully explanted. By now, the patient was successfully discharged from the hospital

with no sign of transplant rejection and is recovering in a rehabilitation clinic because of the preoperative neurological complications related to the LVAD therapy.

IGM-IVIG application

In all patients, IGM-IVIG (Pentaglobin®, Biotest AG, Dreieich, Germany) was applied with a total dose concentration of 0.5 to 1.0 g/kg bodyweight as a continuous venous infusion for three consecutive days. Patients were selected for IGM-IVIG application in case confirmed severe AMR (P1), severe symptoms (P1 and 4), or relevant circulating anti-HLA-antibodies with MFI $>$ 5000 (P2 and 3).

Immunosuppression

Immunosuppressive regime primary consisted of a combination therapy of prednisolone, tacrolimus, and mycophenolate mofetil in all patients. No additional antibody induction therapy was applied.

Discussion

In this small case series, we summarized our expertise of the treatment of DSA-MR after HTx with IGM-IVIG. Although the study population covers only four patients, we presented cases of patients of different gender, age, medical history, onset of DSA-MR, as well as clinical implications. As in every case report, findings are still preliminary, and large randomized controlled studies are needed to prove our findings; however, by now, we did not observe a single severe adverse effect of the treatment with IGM-IVIG and every patient recovered after the application which is quite promising for the future.

While patient P1 and P4 experienced severe malign arrhythmia related to the DSA-MR, the other two patients were more or less clinical unaffected, and DSA-MR was an incidental finding after routine diagnostics for organ rejection. Both presentations represent typical cases of DSA-MR, which covers a wide range of potential clinical implications and is reported to affect the hemodynamic in 10% to 47% of cases.[16] This might be related to the large variety of different DSA against donor HLA that are by now reported in the literature.[3,5,16] Because of the different expressions of HLA antigens in the human cells, different DSA are able to affect different targets and therefore cause different clinical implications.[5] Nonetheless, all kinds of DSA-MR are related to an increased risk of the development of cardiac allograft vasculopathy.[3,5,16]

Two of the reported patients experienced an early onset of DSA-MR during the initial HTx hospital, which is a typical period according to the literature.[16] In contrast to that, P3 developed DSA-MR about one and a half year after the HTx. Clerkin *et al*.[17] reported that this kind of late-onset DSA-MR is associated with an increased risk of mortality due to an even more rapid and severe development of cardiac allograft vasculopathy compared with DSA-MR within the early post-operative period.

Presence of DSA against donor HLA was confirmed in P2–P4, and in P4, endomyocardial biopsies did not show typical signs of AMR (pAMR0). However, because of the heterogeneous characteristics of DSA-MR, it is not unlikely to detect only the DSA or the AMR.[2,4,18] Furthermore, three patients of our cohort were on previously LVAD support, which is related to sensitization and an increase in HLA antibodies.[19,20]

While IVIG therapy is mainly related to headache, fever, rigour, and myalgia, application of IGM-IVIG in sepsis patients was also related to thromboembolic events caused by hyperviscosity syndrome and acute renal failure.[14,16] However, we did not observe any serious adverse event related to the application of IGM-IVIG.

After multimodal therapy of DSA-MR with application of IGM-IVIG ventricular function of all reported patients recovered, histopathological findings improved, and all patients could successfully be discharged from the hospital, which is superior to the most reported therapy protocols by now.[2,4,6,7,16]

Conclusion

Diagnosis and treatment of DSA-MR remains challenging in the postoperative care of patients undergoing HTx. As part of a multimodal therapy, application of IGM-IVIG offers promising results in the handling of DSA and DSA-MR. Although large randomized controlled studies are needed, therapy with IGM-IVIG seems to be safe and effective and should be kept in mind for future therapy strategies focusing on DSA and DSA-MR after solid organ transplantation.

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Conflict of interest

The authors have nothing to declare.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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