JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
CASE REPORT

A unique profile of insulin antibody titer in islet-transplanted patients

Yamato Keidai[1], Junji Fujikura[1], Toshihiro Nakamura[1], Takayuki Anazawa[2], Ryo Ito[1], Masahito Ogura[1], Etsuro Hatano[2], Nobuya Inagaki[1]*

[1]Department of Diabetes, Endocrinology and Nutrition, Graduate School of Medicine, Kyoto University, Kyoto, Japan, and [2]Division of Hepato-Biliary-Pancreatic Surgery and Transplantation, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Keywords
Immunosuppression therapy, Insulin antibodies, Islet transplantation

***Correspondence**
Nobuya Inagaki
Tel.: +81-75-751-3560
Fax: +81-75-751-4244
E-mail address:
inagaki@kuhp.kyoto-u.ac.jp

J Diabetes Investig 2022; 13: 1939–1942

doi: 10.1111/jdi.13878

ABSTRACT

Insulin antibodies (IAs) can cause glycemic variability. Islet transplantation (ITx) is a treatment for insulin-deficient diabetes that aims to establish on-target glycemic control in the absence of hypoglycemia. To date, there has not been a detailed case study of the association between ITx and IA levels. In this study, we identified a unique profile of IA titers, which differed from glutamic acid decarboxylase antibody titers, in four ITx patients. IA levels decreased with intensified immunosuppressive therapy, whereas glutamic acid decarboxylase antibodies increased transiently after ITx. These data suggest the possibility that IAs, unlike other islet autoantibodies, were eliminated due to immunosuppression after transplantation therapy. The disappearance of IAs, as well as the restoration of regulated insulin secretion after ITx, might have a positive effect on glycemic control in recipients with diabetes. Furthermore, this unique feature is suggestive of immunological pathogenesis and has implications for the treatment of IA-causing disease conditions.

INTRODUCTION

Insulin antibodies (IAs) are classified into autoantibodies against endogenous insulin and antibodies against exogenous insulin. Autoantibodies to endogenous insulin are frequently observed at the onset of type 1 diabetes and can predict the development of type 1 diabetes.[1] In rare cases, in patients without diabetes with no history of insulin exposure, the autoantibodies cause prolonged hypoglycemia, a condition known as 'insulin autoimmune syndrome'. IAs against exogenous insulin develop after exposure of patients with diabetes administered insulin. High titers of IA can cause insulin ineffectiveness and hyperglycemia in some patients with diabetes,[2–4] but the clinical impact of IAs on glycemic control is unknown.[5]

Islet transplantation (ITx) has become an established treatment for type 1 diabetes.[6] ITx has been covered by health insurance in Japan since 2020, but few reports exist on changes in IA titers before and after ITx. Monitoring islet-associated antibodies in islet-transplanted patients can help estimate the immune status of the recipient and also predict immune events, such as the recurrence of type 1 diabetes and rejection. In previous studies of islet autoantibodies, including the glutamic acid decarboxylase antibody (GADA), insulinoma-associated antigen-2 antibody and zinc transporter 8 antibody, post-transplant increases in the titers were found to be associated with lower graft survival.[7–9] In this report, we describe the unique profile of IA titers in four ITx cases, which differs from that of GADA. IA levels decreased with intensified immunosuppressive therapy, whereas GADA levels increased transiently after ITx.

Received 14 February 2022; revised 17 June 2022; accepted 22 June 2022

CASE REPORT

Patient 1 was diagnosed with type 1 diabetes at the age of 40 years, and received an ITx at the age of 59 years, followed by a second ITx 7 months later. Patient 2 was diagnosed with type 1 diabetes at the age of 23 years, and her first ITx was carried out at the age of 56 years. The second and third ITxs were carried out 5 and 19 months after the first ITx. They were naïve to immunosuppressive therapy at the first ITx, and were positive for IAs and GADAs. The initial induction regimen of immunosuppression was antithymocyte globulin and etanercept. The maintenance regimen was tacrolimus and mycophenolate mofetil (MMF). In patient 1, 2 years after the first ITx, their glycated hemoglobin reduced from 8.4 to 7.7%, and the daily subcutaneous insulin injection dose decreased from 0.57 to

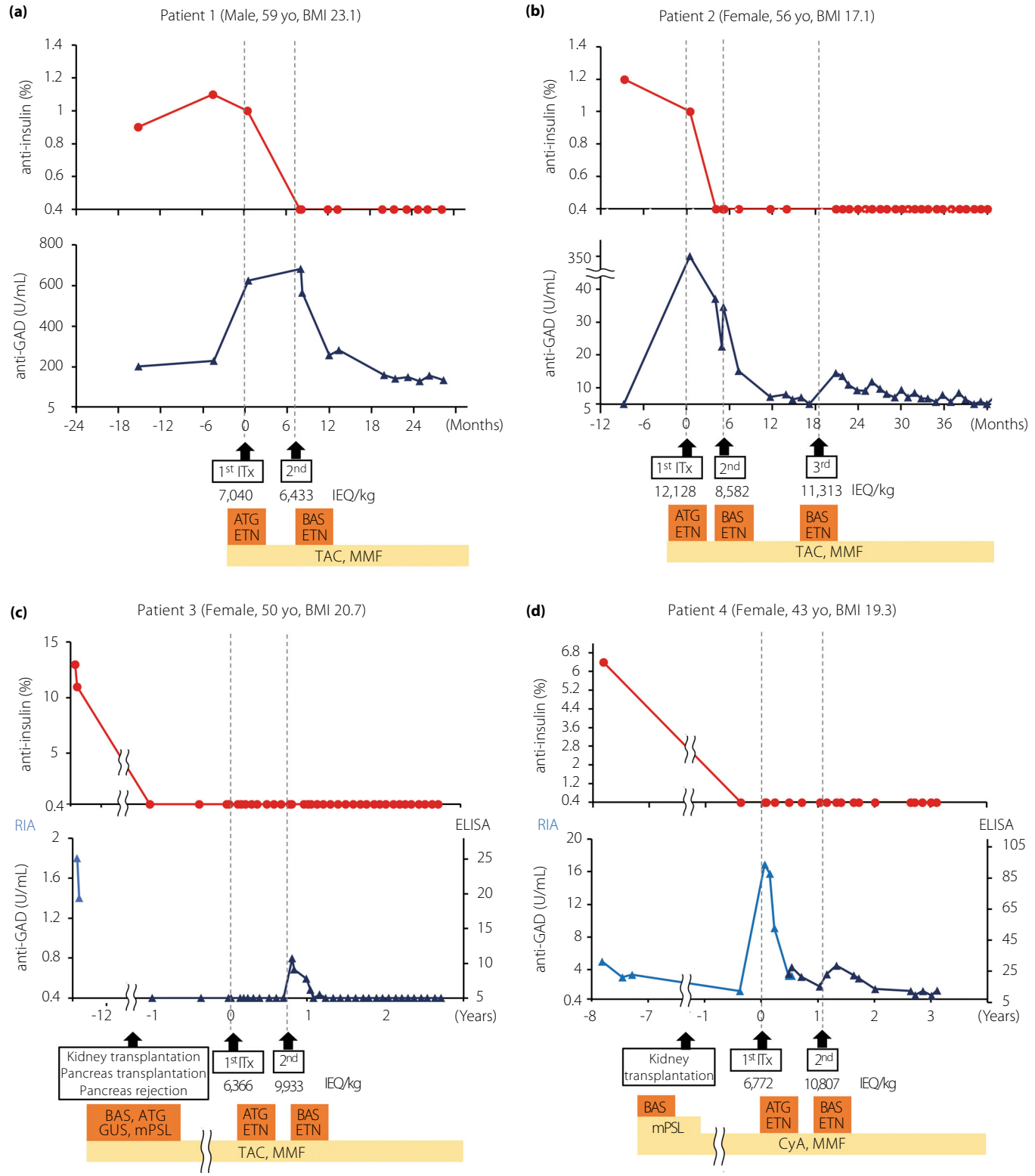

Figure 1 | Changes in insulin antibody and glutamic acid decarboxylase antibody (GADA) titers before and after islet transplantation (ITx) in (a) patient 1, (b) patient 2, (c) patient 3 and (d) patient 4. The horizontal axis shows the period since the first ITx. The information at the top represents the age and body mass index (BMI) at the time of the first ITx. At the bottom, the immunosuppressive agents used for ITx are shown. The regimens in orange boxes show the induction or anti-rejection therapy. The regimens in yellow boxes show the maintenance therapy. ATG, anti-thymocyte globulin; BAS, basiliximab; CyA, cyclosporin; ELISA, enzyme-linked immunosorbent assay; ETN, etanercept; GUS, gusperimus; MMF, mycophenolate mofetil; mPSL, methylprednisolone; TAC, tacrolimus.

0.46 U/kg. In patient 2, their glycated hemoglobin reduced from 8.4 to 5.7%, and the daily insulin dose decreased from 0.50 to 0.13 U/kg (Table S1). In these patients, GADA levels showed a transient increase after each ITx, whereas notably, IAs became negative after the ITx (Figure 1a,b).

Patient 3 was diagnosed with type 1 diabetes at the age of 13 years, received a living kidney transplantation at the age of 38 years and a brain-dead pancreas transplantation at the age of 43 years. Although this patient was positive for IAs before kidney transplantation, they became negative after immunosuppression therapy comprising antithymocyte globulin, etanercept and basiliximab throughout the kidney and pancreas transplantation, and the suspected pancreas rejection. The patient had an ITx at the age of 50 years, followed by a second ITx 9 months later. After the ITxs, GADA transiently increased, whereas IA did not increase and remained negative (Figure 1c).

Diagnosed with type 1 diabetes at the age of 12 years, patient 4 also received a living kidney transplantation at the age of 37 years before ITx. The induction regimen for the kidney transplantation was basiliximab, which was followed by a maintenance regimen of cyclosporin, MMF and methylprednisolone. Although IAs were present before the kidney transplantation, they became negative afterwards. After subsequent ITxs, GADA levels showed a transient increase, but IAs remained negative (Figure 1d).

After ITxs, no patients have reported an episode of severe hypoglycemia.

DISCUSSION

Here, we report a unique profile of IAs in four ITx patients. In two of the cases, IAs were positive before the ITx and became negative afterward. In the other two cases, IAs were positive before kidney or pancreas transplantation, and were negative afterward and remained undetected after subsequent ITxs. In all four cases, IAs showed a distinct and different profile to GADAs during the course of ITxs. Elevations in the levels of islet autoantibodies against GAD, insulinoma-associated antigen-2 or zinc transporter 8 have frequently been observed after ITx,[7–9] which presumably reflects an immune response to the islet graft. In the present cases, no significant correlation was observed between GADA titer and secretory units of islets in transplantation, an index of β-cell function, for combined data collected from all four patients, although a weak positive correlation was observed for data from a single patient (patient 3, $R = 0.456$, $P = 0.038$; Figures S1 and S2).

The difference between IAs and other islet autoantibodies might be associated with the fact that IAs can be produced against endogenous insulin and against exogenously administered insulin. Regarding the clinical impact of IA, in some rare cases, it has been reported that prominent levels of IA antibodies can cause poor glycemic control.[2–4] However, the clinical impact of IA on glycemic control has generally not been observed,[5] and it is unclear whether decreases in IA titers in the present cases contributed to improved glycemic control.

For the candidate lowering IA titers, some case reports showed that immunosuppressive therapy, such as MMF and rituximab, effectively reduces IA levels in patients with high IA titers who develop insulin ineffectiveness.[2–4] On the contrary, in the context of ITx, one previous report showed that positivity for IAs was stable both before and after ITx, under the original Edmonton immunosuppression regimen; that is, the combination of daclizumab, sirolimus and tacrolimus.[10] This discrepancy suggests recent advanced immunotherapies, such as antithymocyte globulin, basiliximab, etanercept and MMF, might effectively lower IA titers.

Unlike other islet autoantibodies, IAs can be eliminated after transplantation therapy due to modern immunosuppression. We expect that the finding of diminishing IAs will help us manage future cases with high IA titers, and provide insights into how to regulate the autoantibody reaction. Furthermore, these characteristic trends are of interest in view of the production mechanisms of antibodies associated with diabetes mellitus.

ACKNOWLEDGMENTS

The authors thank all of the clinical staff who participated in the treatment of the patients.

DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: Islet transplantations in this study were carried out following the clinical trial "Islet transplantation using brain-dead donors and donors after cardiac death for patients with insulin-dependent diabetes mellitus suffering from complicating hypoglycemia unawareness" (UMIN000003977). The research protocol was approved by the institutional review boards of Kyoto University.

Informed consent: Written informed consent was obtained from all patients.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

REFERENCES

1. Regnell SE, Lernmark A. Early prediction of autoimmune (type 1) diabetes. *Diabetologia* 2017; 60: 1370–1381.
2. Segal T, Webb E, Viner R, *et al*. Severe insulin resistance secondary to insulin antibodies: successful treatment with the immunosuppressant MMF. *Pediatr Diabetes* 2008; 9: 250–254.
3. Jassam N, Amin N, Holland P, *et al*. Analytical and clinical challenges in a patient with concurrent type 1 diabetes, subcutaneous insulin resistance and insulin autoimmune syndrome. *Endocrinol Diabetes Metab Case Rep* 2014; 2014: 130086.
4. Hao JB, Imam S, Dar P, *et al*. Extreme insulin resistance from insulin antibodies (not insulin receptor antibodies) successfully treated with combination immunosuppressive therapy. *Diabetes Care* 2017; 40: e19–e20.

5. Fineberg SE, Kawabata TT, Finco-Kent D, *et al*. Immunological responses to exogenous insulin. *Endocr Rev* 2007; 28: 625–652.
6. Nakamura T, Fujikura J, Inagaki N. Advancements in transplantation therapy for diabetes: pancreas, islet and stem cell. *J Diabetes Investig* 2021; 12: 143–145.
7. Jaeger C, Brendel MD, Hering BJ, *et al*. Progressive islet graft failure occurs significantly earlier in autoantibody-positive than in autoantibody-negative IDDM recipients of intrahepatic islet allografts. *Diabetes* 1997; 46: 1907–1910.
8. Bosi E, Braghi S, Maffi P, *et al*. Autoantibody response to islet transplantation in type 1 diabetes. *Diabetes* 2001; 50: 2464–2471.
9. Piemonti L, Everly MJ, Maffi P, *et al*. Alloantibody and autoantibody monitoring predicts islet transplantation outcome in human type 1 diabetes. *Diabetes* 2013; 62: 1656–1664.
10. Lablanche S, Borot S, Thaunat O, *et al*. Impact of anti-insulin antibodies on islet transplantation outcome: data from the GRAGIL network. *Transplantation* 2014; 98: 475–482.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | Correlation between glutamic acid decarboxylase antibody titers and secretory units of islets in transplantation.

Figure S2 | Changes in secretory units of islets in transplantation after islet transplantations in each patient.

Table S1 | Clinical features of four patients.