Improvement of Glucose Control and Reduction of Hypoglycemia Following Intravenous Immune Globulins in a Child With Type 1 Diabetes and High Levels of Insulin Antibodies

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Diabetes Care 2017;40:e69–e70 | https://doi.org/10.2337/dc16-2420

Anti-insulin antibodies (AIA) usually have no impact on glucose control in type 1 diabetes (1). However, high titers of AIA with low/medium affinity for insulin may form unstable immune complexes resulting in high glucose variability (2). Corticosteroids, plasmapheresis, mycophenolate mofetil (3), and rituximab (4) have been tried to solve this issue. We report a case of interest owing to significant improvement following intravenous infusions of human immune globulins (IVIg).

A lean 8-year-old Caucasian boy was diagnosed with type 1 diabetes 3 years before being referred to our clinic. No autoantibodies against islet antigens, GAD, IA2, or zinc transporter 8 were detected, but testing for AIA was not done at onset and no *GCK*, *HNF1A*, *HNF4A*, *HNF1B*, *ABCC8*, *KCNJ11,* or *INS* gene mutations were found. Under multiple daily insulin injections or an insulin pump, high glucose variability included uncontrollable postmeal hyperglycemia and recurrent severe hypoglycemia in fasting/nighttime periods. Despite a sensor-augmented pump during the previous 15 months, glucose swings remained unaffected. HbA_{1c} moved from 8.9% (74 mmol/mol) 9 months before IVIg to 8.4% (68 mmol/mol) 5 months and immediately before IVIg.

When the child was admitted to our clinic, his high plasma insulin levels were discordant with insulin pump delivery rates while managed by hospital nurses, and a high AIA level was found (49.8%; reference 0–5.5%; radioimmunoassay: AAI, Cisbio, Gif-sur-Yvette, France). Hence, AIA were suspected in the failure of glucose control. Similar to the treatment of idiopathic thrombocytopenic purpura and based upon a previous report (5), IVIg (Clairyg, LFB Biomédicaments, Les Ulis, France) of 0.4 g/kg/day were administered for 5 consecutive days without any side effects. The AIA titer fell to 27.8%, 30.7%, and 22.9% after 1, 3, and 7 months, respectively. HbA_{1c} was 8.1% (65 mmol/mol) after 3 months, with a significant increase in the average daily percentage of time spent with sensor glucose in the 3.9–10 mmol/L target range thanks to a similar decrease in the percentage of time spent above 10 mmol/L and a dramatic reduction in the percentage of nights with at least one hypoglycemic event; the mean of daily differences (best index for estimating between-day glycemic variability) was reduced, albeit not significantly (Fig. 1). After 7 months, HbA_{1c} further decreased to 7.8% and hypoglycemia only occurred in 8.3% of monthly nights.

IVIg have been used as immune-modulating agents in pathological conditions involving autoantibodies, with a mode of action mainly based upon their binding to idiotypic antibodies, thus allowing their clearance by the reticuloendothelial system. In our case, we speculate that AIA could have been cleared after binding to IVIg as a first effect. However, the sustained effect that exceeded the lifetime of IVIg, also observed by Hanaire-Broutin et al. (5), suggests that a further action was induced on the production of AIA by the specific B cells and/or on the regulation of the immune process by T cells. Of note, while IVIg were followed by a dramatic reduction of daily insulin doses in the patient described by Hanaire-Broutin et al. (5), the dose remained stable in our patient, suggesting the effects of AIA on insulin availability were different. Further patient follow-up will assess whether improved glucose control is maintained.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.
Author Contributions. L.M. and E.R. provided active care during the reported patient's hospital course and follow-up, researched the data, performed data analysis, and wrote the manuscript. P.L., F.D.-V., and A.F. provided active care during the reported patient's hospital course and contributed to data collection and drafting of the manuscript. J.P. conducted statistical data analysis. E.R. is the guarantor of this work

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Received 13 November 2016 and accepted 12 March 2017.

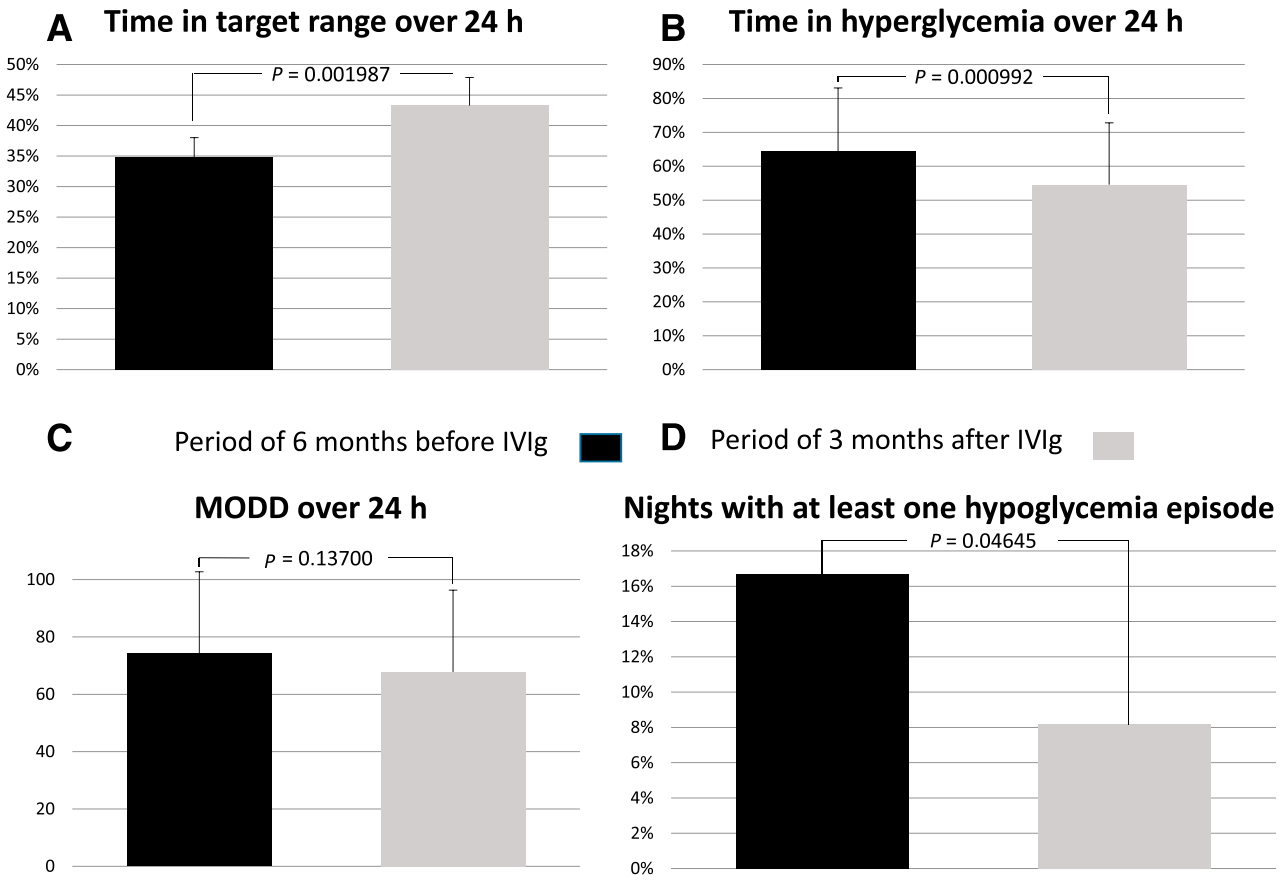

Figure 1—Continuous glucose monitoring metrics in a patient with type 1 diabetes and high AIA titers 6 months before and 3 months after IVIg. *A*: Percentage of time (mean ± SD) in target glucose range (3.9–10 mmol/L) over 24 h. *B*: Percentage of time (mean ± SD) in hyperglycemia (>10 mmol/L) over 24 h. *C*: Mean ± SD of daily differences (MODD) over 24 h. *D*: Percentage of nights with at least one episode of hypoglycemia (<3.9 mmol/L). The data for the two periods were collected with an Enlite Glucose Sensor (Medtronic, Northridge, CA). *P* values were calculated using a two-tailed Mann-Whitney *U* test.

and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Schernthaner G. Immunogenicity and allergenic potential of animal and human insulins. Diabetes Care 1993;16(Suppl. 3):155–165
2. Radermecker RP, Renard E, Scheen AJ. Circulating insulin antibodies: influence of continuous subcutaneous or intraperitoneal insulin infusion, and impact on glucose control. Diabetes Metab Res Rev 2009;25:491–501
3. Segal T, Webb E, Viner R, Pusey C, Wild G, Allgrove J. Severe insulin resistance secondary to insulin antibodies: successful treatment with the immunosuppressant MMF. Pediatr Diabetes 2008;9:250–254
4. 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.
5. Hanaire-Broutin H, Melki V, Tauber JP. Treatment of acquired immune insulin resistance with i.v. immunoglobulins. Diabetologia 1999; 42:1378