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Low-Dose Antithymocyte Globulin: A Pragmatic Approach to Treating Stage 2 Type 1 Diabetes

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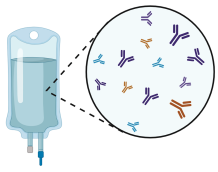
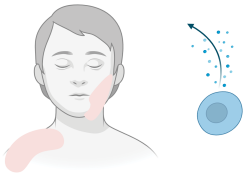
A repurposed and relatively inexpensive disease-modifying therapeutic in stage 2 type 1 diabetes (T1D): low-dose anti-thymocyte globulin (ATG)



Intervention

Low-dose ATG
given off-label
6 Children ages 5-14 yrs
17% Female
All Stage 2 T1D:
Multiple
Autoantibodies +
Dysglycemia



Transient Side Effects

Cytokine release
syndrome (3/6)
Lymphopenia (6/6)
Serum sickness (6/6)
treated with 3-4 days oral
prednisone
Nausea (3/6)
Rash (5/6)

Clinical Outcomes

3 Remained in
Stage 2 T1D

HbA1c 5.0 - 6.1%
Time in range 91-100%
Follow up 18 mos - 4 years

3 Progressed to
Stage 3 T1D

HbA1c 5.1 - 5.6%
Time in range 88 - 93%
Follow up 18 mos

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  The families of six children with stage 2 type 1 diabetes made unprompted requests for therapeutics outside the constraints of clinical trials.
- **What is the specific question(s) we wanted to answer?**
  Does off-label low-dose antithymocyte globulin (ATG), given as part of clinical therapy, slow disease progression?
- **What did we find?**
  Progression to stage 3 did not occur after at least 18 months of follow-up in three of six (50%) children. The three patients who progressed to stage 3 maintained HbA_{1c} below target with low insulin requirements and robust stimulated C-peptide through 18 months postdiagnosis.
- **What are the implications of our findings?**
  Given the economical and logistical benefits of low-dose ATG, fully powered studies of low-dose ATG in stage 2 type 1 diabetes patients are warranted.

Low-Dose Antithymocyte Globulin: A Pragmatic Approach to Treating Stage 2 Type 1 Diabetes

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BRIEF REPORT

OBJECTIVE

Low-dose antithymocyte globulin (ATG) (2.5 mg/kg) preserves C-peptide and reduces HbA_{1c} in new-onset stage 3 type 1 diabetes, yet efficacy in delaying progression from stage 2 to stage 3 has not been evaluated.

RESEARCH DESIGN AND METHODS

Children (*n* = 6) aged 5–14 years with stage 2 type 1 diabetes received off-label, low-dose ATG. HbA_{1c}, C-peptide, continuous glucose monitoring, insulin requirements, and side effects were followed for 18–48 months.

RESULTS

Three subjects (50%) remained diabetes free after 1.5, 3, and 4 years of follow-up, while three developed stage 3 within 1–2 months after therapy. Eighteen months posttreatment, even disease progressors demonstrated near-normal HbA_{1c} (5.1% [32 mmol/mol], 5.6% [38 mmol/mol], and 5.3% [34 mmol/mol]), time in range (93%, 88%, and 98%), low insulin requirements (0.17, 0.18, and 0.34 units/kg/day), and robust C-peptide 90 min after mixed meal (1.3 ng/dL, 2.3 ng/dL, and 1.4 ng/dL).

CONCLUSIONS

These observations support additional prospective studies evaluating ATG in stage 2 type 1 diabetes.

Type 1 diabetes involves the T-cell–mediated destruction of insulin-producing β-cells, resulting in lifelong dependence on exogenous insulin (1). The disease progresses through stages defined by two or more islet autoantibodies (stage 1), glycemic dysregulation (stage 2), and finally clinical diagnosis (stage 3) (2). To date, only teplizumab (anti-CD3) has demonstrated, on a large scale, capacity to delay progression from stage 2 to stage 3 (3); however, at least nine immunotherapeutics have shown potential for preserving C-peptide in stage 3 (4–12). One such agent, low-dose antithymocyte globulin (ATG) (2.5 mg/kg), preserved β-cell function and reduced HbA_{1c} for at least 2 years in stage 3 trial participants (9,13). Like teplizumab, we believe low-dose ATG may preserve β-cell function and delay disease progression in stage 2. Here, we report on six children with stage 2 diabetes treated with low-dose ATG as part of clinical care. No other immunotherapeutic studies were available to these patients in the U.S. at the time of treatment (2019–2021).

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RESEARCH DESIGN AND METHODS

Stage 2 Type 1 Diabetes Diagnosis

Six children had a first-degree relative with type 1 diabetes and were screened for risk through TrialNet (14). TrialNet initially tests for autoantibodies specific to insulin (mIAA) and glutamic acid decarboxylase 65 (GADA). Samples positive for mIAA were tested for autoantibodies to insulinoma-associated protein 2 (IA2A), zinc transporter 8 (ZnT8A), and islet cell cytoplasmic autoantigen (ICA); samples positive for GADA were tested for IA2A and ZnT8A. All six patients had two or more autoantibodies confirmed on two separate samples, underwent oral glucose tolerance test (OGTT), and had HbA_{1c} measured. Stage 2 was defined by *1*) fasting plasma glucose $\geq$100 mg/dL but $<$126 mg/dL, *2*) 30-, 60-, or 90-min glucose level $\geq$200 mg/dL during OGTT, *3*) 120-min glucose $>$140 mg/dL but $<$200 mg/dL during OGTT, or *4*) HbA_{1c} $\geq$5.7% (39 mmol/mol) but $<$6.5% (48 mmol/mol) (2). This case series represents a small fraction of stage 2 subjects followed by our team. Each patient's family made unprompted requests for information regarding therapeutics available outside the constraints of clinical trials. Risks, benefits, and alternatives to off-label ATG as a clinical therapeutic were reviewed, and consent/assent was documented.

Treatment

Prior to treatment, complete blood counts with differentials, serum chemistries, liver function tests, tuberculosis testing, HIV antibodies, hepatitis B and C antibodies, cytomegalovirus antibodies and PCR, and Epstein-Barr virus antibodies and PCR were obtained. All six patients had normal laboratory screens and negative Epstein-Barr virus PCR within 2 weeks of treatment. Acetaminophen (10 mg/kg, maximum 650 mg orally), diphenhydramine (1.25 mg/kg, maximum 50 mg intravenously [i.v.]), and methylprednisolone (0.25 mg/kg i.v.) were administered immediately before ATG. ATG (thymoglobulin) was prepared with heparin (1,000 units) and hydrocortisone (20 mg) to minimize risk for thrombophlebitis and infused through a peripheral i.v. route over a minimum of 6 h on day 1 and 4 h on day 2 (day 1, 0.5 mg/kg; day 2, 2.0 mg/kg) in our outpatient pediatric infusion center. Commercial insurance covered the costs of treatment and follow-up laboratory studies, with only one insurer requiring a prior authorization. The maximum out-of-pocket cost for treatment was $1,500 USD.

Follow-up

Incidence and severity of infusion-related cytokine release syndrome (CRS) and serum sickness (SS) were assessed using Common Terminology for Adverse Events (CTCAE) version 5 (15). Any patient receiving steroids for SS management was assigned grade 3. HbA_{1c}, insulin use, insulin dose–adjusted HbA_{1c} ($IDAA_{1c}$), and continuous glucose monitor (CGM) time in range (TIR) between 70 and 180 mg/dL were collected clinically. For a less invasive alternative to 2-h mixed-meal tolerance test area under the curve (16), C-peptide values 90 min after mixed meal were obtained every 3–6 months. Patients who declined mixed-meal stimulation had fasting C-peptide measured. Stage 3 type 1 diabetes was diagnosed according to established clinical criteria (17).

RESULTS

Six patients, aged 5–14 years, with stage 2 type 1 diabetes received a 2-day course of low-dose ATG (2.5 mg/kg). Patient demographic, biochemical, and clinical outcomes data are presented in Table 1 and Fig. 1. Of the six patients treated with low-dose ATG, three (50%) did not progress to stage 3 by 18 months, 3 years, and 4 years of post-ATG follow-up. Of the three patients who progressed to stage 3, the diagnosis was made 1–2 months post-ATG treatment, with all three maintaining low insulin requirements, $IDAA_{1c}$ $<$7, low HbA_{1c}, near-normal CGM metrics (high TIR, low coefficient of variation, and low hypoglycemia), and robust C-peptide values. Grade 1 CRS occurred in three of six (50%) and grade 3 SS occurred in all six (100%) patients. There were no adverse events related to CRS or SS beyond the first 2 weeks post-ATG, and no secondary infections were reported post-ATG treatment. Most patients were treated during the coronavirus disease 2019 (COVID-19) pandemic at times when patients and their families were sequestering at home to reduce risk of exposure. No COVID-19 infections were reported during the 3 months following infusion, and no concerning infections were reported during follow-up.

Case 1

An 8-year-old female, whose father had type 1 diabetes, tested positive for five islet autoantibodies. HbA_{1c} was 4.9% (30 mmol/mol). OGTT confirmed stage 2 with 90-min glucose of 205 mg/dL and 2-h glucose of 101 mg/dL. Grade 1 CRS with nausea and muscle cramping was noted on day 1 of ATG infusion, requiring a temporary infusion rate reduction and ondansetron (4 mg i.v.) for nausea. SS, denoted by maculopapular erythematous rash and moderate arthralgia, developed 9 days postinfusion. Given prior experiences with treating SS and parents' desire to minimize symptoms, a 4-day course of oral prednisone (30 mg twice per day [b.i.d.]) was given, with full resolution of symptoms. After 4 years of follow-up, she had not progressed to stage 3.

Case 2

A 5-year-old male, whose sibling had type 1 diabetes, had five positive islet autoantibodies and HbA_{1c} was 5.4% (36 mmol/mol). OGTT revealed dysglycemia, with 60- and 90-min glucose values of 234 mg/dL and 214 mg/dL, respectively. Grade 1 CRS occurred on day 2 of ATG infusion, requiring treatment with ketorolac (0.5 mg/kg i.v.) for headache and muscle cramping and ondansetron (4 mg i.v.) for nausea. Ten days following ATG infusion, he developed maculopapular rash, general malaise, and temperature of 38°C. His family requested treatment of SS, and a 3-day course of oral prednisone (30 mg b.i.d.) was provided, with complete resolution of symptoms after 72 h. After 3 years of follow-up, he had not progressed to stage 3.

Case 3

A 13-year-old male, whose sibling had type 1 diabetes, was positive for three islet autoantibodies. OGTT revealed dysglycemia with 2-h glucose of 197 mg/dL. Baseline HbA_{1c} was 6.5% (48 mmol/mol), which is concerning for late stage 2 type 1 diabetes. Despite the borderline HbA_{1c}, he was included in this case series given the lack of symptoms, confirmatory HbA_{1c}, or OGTT to confirm stage 3. He did not experience CRS but did have SS, denoted by a pruritic maculopapular rash, finger swelling, and arthralgia that occurred 10 days post-ATG. Three days of oral prednisone (50 mg b.i.d.) resulted in complete resolution of symptoms. After 18 months of follow-up, he had not progressed to stage 3.

Table 1—Demographic and clinical values for patients at baseline and over time

Patient	Age, race, sex, BMI (%)	Proband	Autoantibodies present at staging	OGTT blood glucose levels (mg/dL) at stage 2 diagnosis	CRS and SS grade	WBC (1,000/mm^3) and lymphocyte (%)†	Drug-related AEs post-CRS/SS	Pre- and post-ATG time points	HbA_{1c}, % (mmol/mol)	90-Min post-MMTT-stimulated C-peptide (ng/mL)	Insulin use (units/kg/day)	$IDAA_{1c}$ (HbA_{1c} + 4× insulin dose) (units/kg/day)	Most recent CGM TIR (70–180 mg/dL) (%)
Case 1	8	Father	mIAA	88, 0 min	Grade 1 CRS	6.4/5.7	None	Pre-ATG	4.9 (30)	NO	0	4.9	
	W		GADA	107, 30 min	Grade 3 SS	56/40		1 year	5.6 (38)	3.1		5.6	
	F		IA2A	124, 60 min				2 years	5.3 (34)	2.1		5.3	98–100
	14.8 (24)		ZNT8A	205, 90 min				3 years	5.2 (33)	NO		5.2	
			ICA	101, 120 min				4 years	5.4 (36)	1.9		5.4	
Case 2	5	Sibling	mIAA	98, 0 min	Grade 1 CRS	5.9/6.0	None	Pre-ATG	5.4 (36)	NO	0	5.4	
	W		GADA	115, 30 min	Grade 3 SS	45/54		1 year	5.1 (32)	11.4		5.1	89–100
	M		IA2A	234, 60 min				2 years	5.4 (36)	3.3		5.4	
	13.6 (3)		ZNT8A	214, 90 min				3 years	5.0 (31)	2.0		5.0	
			ICA	193, 120 min									
Case 3	13	Sibling	GADA	95, 0 min	No CRS	5.9/6.3	None	Pre-ATG	6.5 (48)	NO	0	6.5	
	W		IA2A	197, 120 min	Grade 3 SS	40.4/43		6 months	6.2 (44)	NO		6.2	
	M		ZnT8A					9 months	6.3 (45)	NO		6.3	86–91
	25.4 (87)							1 year	6.3 (45)	NO		6.3	
								18 months	6.1 (43)	NO		6.1	
Case 4	8	Father and sibling	mIAA	110, 0 min	Grade 1 CRS	3.8/8.1	None	Pre-ATG	5.8 (40)	NO	0	5.8	
	W		GADA	158, 30 min	Grade 3 SS	50.3/39.7		1 month	7.0 (53)*	NO	0.10	7.4	
	M		IA2A	184, 60 min				6 months	5.9 (41)	0.9#	0.15	6.5	95–98
	14.8 (16)		ZNT8A	194, 90 min				9 months	6.1 (43)	NO	0.16	6.7	
				178, 120 min				1 year	5.5 (37)	1.2	0.21	6.3	
								18 months	5.1 (32)	1.3	0.17	5.8	
Case 5	14	Sibling	GADA	102, 0 min	No CRS	4.3/4.7	None	Pre-ATG	5.9 (41)	1.2	0	5.9	
	W		IA2A	156, 30 min	Grade 3 SS	33/45		2 months	6.5 (48)*	2.5	0.15	7.1	
	M		ZnT8A	193, 60 min				3 months	6.1 (43)	2.0	0.10	6.5	83–86
	23.1 (95)			211, 90 min				6 months	5.0 (31)	2.3	0.10	5.1	
				165, 120 min				1 year	5.8 (40)	NO	0.15	6.4	
								18 months	5.6 (38)	NO	0.19	6.4	
Case 6	13	Mother	GADA	113, 0 min	No CRS	3.7/4.6	None	Pre-ATG	5.8 (40)	5.3	0	5.8	
	W		IA2A	153, 120 min	Grade 3 SS	34.3/28.2		1 month	10.1 (87)*	NO	0.30	11.2	
	M		ZnT8A					3 months	7.3 (56)	1.2	0.21	8.1	94–98
	20.1 (79)							6 months	5.7 (39)	1.4	0.32	7.0	
								1 year	5.3 (34)	1.9	0.26	6.3	
								18 months	5.3 (34)	1.4	0.34	6.6	

For each of the six patients with stage 2 type 1 diabetes treated with low-dose ATG, anthropometric and clinical data are presented as the following: age at start of treatment (years), reported race (W, White), sex (M, male; F, female), BMI, BMI for age and sex percentile, type 1 diabetes proband, positive islet autoantibodies (mIAA, insulin; GADA, glutamic acid decarboxylase 65; IA2A, insulinoma-associated protein 2; ZnT8A, zinc transporter 8), blood glucose values at 0, 30, 60, 90, and 120 min following OGTT, acute adverse events (AEs), complete blood count values (WBC [white blood cell count] and percentage of lymphocytes), and long-term AEs (drug-related AEs post-CRS/SS). To the right of the center line, values are reported at baseline and during follow-up post-ATG for HbA_{1c}, 90-min stimulated C-peptide values (MMTT, mixed-meal tolerance test; NO, not obtained), insulin use, and $IDAA_{1c}$ (insulin dose–adjusted A_{1c}). Percentages of TIR from 2 weeks of CGM data with ranges are shown for weeks 1 and 2 after the follow-up date. †Data are given as values at baseline/values at 3 months, with WBC given in the first row and % lymphocytes in the second row. *HbA_{1c} at stage 3. #Fasting.

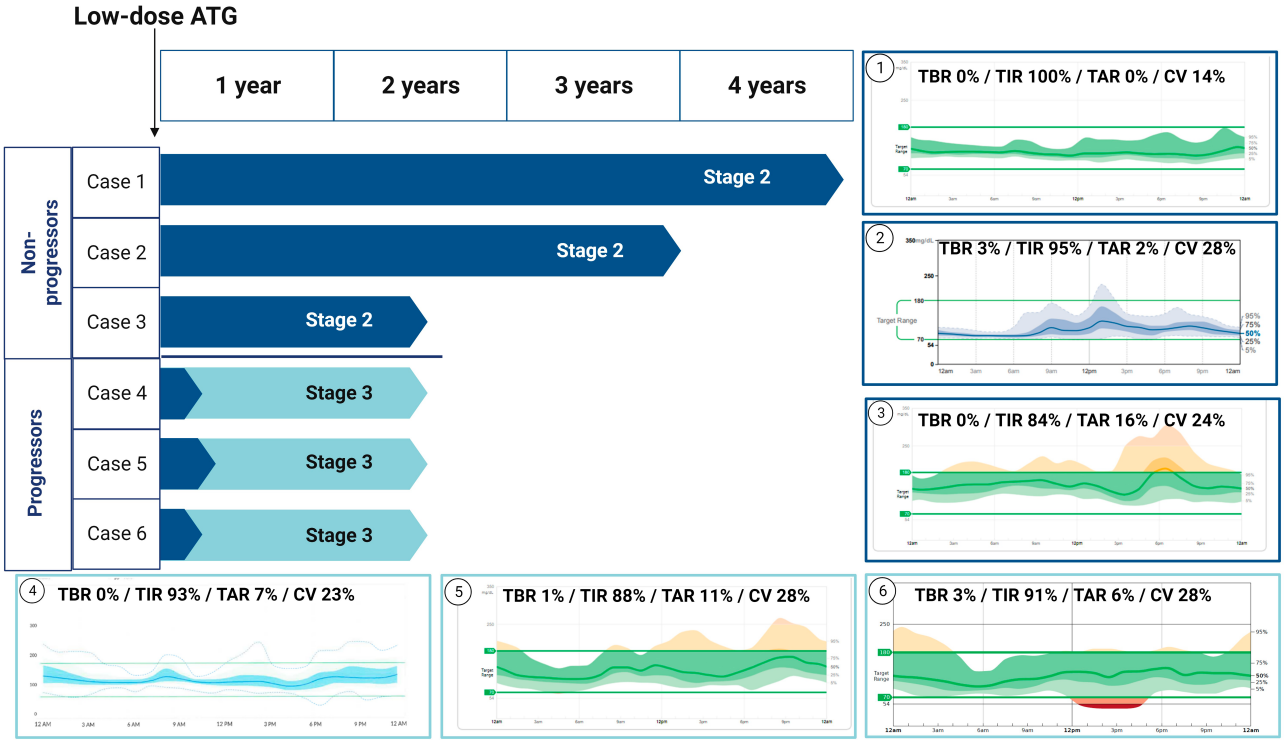

Figure 1—Progression versus nonprogression and CGM metrics in stage 2 ATG recipients. Blue bars demonstrate duration of delay as well as total duration of follow-up (upper left). Notably, all three progressors transitioned to stage 3 within 1–2 months posttreatment. CGM tracings for each subject are shown over a 2-week period at their final documented visit to date, indicating high TIR, low time below range (TBR), low time above range (TAR), and low coefficient of variation (CV) in both nonprogressors (cases 1–3, right) and progressors (cases 4–6, lower).

Case 4

An 8-year-old male, whose father had type 1 diabetes and whose sibling had stage 1 type 1 diabetes, had four islet autoantibodies. Baseline HbA_{1c} was 5.8% (40 mmol/mol). OGTT confirmed dysglycemia with fasting glucose of 110 mg/dL and 2-h glucose of 178 mg/dL. On day two of ATG therapy, grade 1 CRS, denoted by nausea and headache, developed. SS developed on day 9, denoted by a maculopapular rash, arthralgia, and temperature of 38°C. A 4-day course of oral prednisone (30 mg b.i.d.) led to complete resolution of symptoms. One month post-ATG, he developed polyuria and HbA_{1c} of 7% (53 mmol/mol) and was diagnosed with stage 3 type 1 diabetes. Eighteen months post-ATG, his $IDAA_{1c}$ was 5.8 and fasting C-peptide was 2.3 ng/dL.

Case 5

A 14-year-old male, whose sibling had type 1 diabetes, had three islet autoantibodies and HbA_{1c} was 5.9% (41 mmol/mol). OGTT revealed dysglycemia with 90-min glucose of 211 mg/dL and 2-h glucose of 165 mg/dL. CRS did not occur, but SS, denoted by arthralgia and general malaise, presented on day 11 post-ATG. A 3-day course of oral prednisone (30 mg b.i.d.) led to complete resolution of SS. Two months following ATG infusion, persistent postprandial CGM and capillary glucose values >200 mg/dL were documented, polyuria was noted, and stage 3 type 1 diabetes was diagnosed. Low-dose insulin of 0.1 units/kg/day was initiated. Eighteen months post-ATG, $IDAA_{1c}$ was 6.4 and 90-min mixed-meal stimulated C-peptide was 2.3 ng/dL.

Case 6

A 13-year-old male, whose mother had type 1 diabetes, had three islet autoantibodies. OGTT revealed dysglycemia with a fasting glucose of 113 mg/dL and 2-h glucose of 156 mg/dL. While CRS did not occur, SS, denoted by a maculopapular rash, arthralgia, and general malaise, developed 10 days post-ATG. SS was treated with a 3-day course of oral prednisone (30 mg b.i.d.) with complete symptom resolution. One month following ATG, he developed polyuria and hyperglycemia. HbA_{1c} was 10.1% (87 mmol/mol), and stage 3 type 1 diabetes was diagnosed. Eighteen months post-ATG, $IDAA_{1c}$ was 6.6 and 90-min mixed-meal stimulated C-peptide was 1.4 ng/dL.

CONCLUSIONS

Progression to stage 3 type 1 diabetes did not occur after at least 18 months of follow-up in three of six (50%) children with stage 2 type 1 diabetes who received off-label low-dose ATG as part of clinical therapy. Of those who progressed to stage 3, all maintained HbA_{1c} well below target, low insulin requirement ($IDAA_{1c}$ <7), and robust mixed-meal stimulated C-peptide through 18 months postdiagnosis. While a case series of stage 2 subjects is incapable of providing statistically powered observations, the lack of disease progression in a subset of patients and favorable metabolic profiles in the remainder provide proof of concept for the use of low-dose ATG in trials seeking to delay development of type 1 diabetes (18). Additional studies are needed to better understand which individuals are likely to be more responsive to therapy and must include scheduled collection of pre- and posttreatment measures of β-cell function (19). In addition, we must consider the possibility that CRS or SS contributed to the progression to stage 3 in nonresponders. We must also add a note of caution that off-label therapeutics, while commonly used in

pediatric care, should be approached with great caution. Only after pilot and confirmatory data with low-dose ATG were published was this approach considered (9,20).

Low-dose ATG may be an effective, economical (21), and logistically straightforward (2-day infusion) therapy when seeking to prevent or delay progression of type 1 diabetes in high-risk patients. A fully powered study to compare the efficacy of low-dose ATG versus teplizumab would be highly informative, and studies combining therapeutics seeking to provide synergy through complimentary mechanisms of action are needed.

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Duality of Interest. M.J.H. is a member of the scientific advisory board for SAb Biotherapeutics, a company developing a humanized version of ATG and seeking to eliminate SS, and has been a consultant for Sanofi. M.A.A. holds a patent for combination therapies with ATG. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. M.J.H. treated the patients, collected the data, conceived of the case series, drafted and edited the final version, and is responsible for the final manuscript. T.P.F., L.M.J., B.B., and D.A.S. provided care to these patients and edited the manuscript. C.S., J.H., A.C., and M.C. aided in collecting data. T.P.F., L.M.J., B.B., C.E.M., C.W., M.A.B., T.M.B., M.A.A., and D.A.S. edited the manuscript and provided guidance in the management of the use of off-label therapies in type 1 diabetes. M.J.H. is the guarantor of this work 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.

M.A.A. is an editor of *Diabetes Care* but was not involved in any of the decisions regarding review of the manuscript or its acceptance.

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