Evaluation of the Clinical Impact of Dapagliflozin Discontinuation as Adjunctive Therapy for Patients With Type 1 Diabetes After Indication Withdrawal: A Two-Center Retrospective Study

José Ignacio Martínez-Montoro,[1,2,3]
María José Picón-César,[1,2,4]
Víctor José Simón-Frapolli,[1]
José Luis Pinzón-Martín,[1,3]
Jorge García-Alemán,[1]
María Durán-Martínez,[5] *and*
Francisco J. Tinahones[1,2,3,4]

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Use of the sodium–glucose cotransporter 2 inhibitor dapagliflozin leads to improvements in glycemic control, weight loss, and decreased insulin requirements in patients with type 1 diabetes (T1D) (1,2). Dapagliflozin was approved by the European Medicines Agency in 2019 as add-on therapy to insulin for the treatment of T1D. However, based on the removal of this indication by AstraZeneca, dapagliflozin has not been authorized for this population since October 2021. Although changes in glycemic outcomes and other important clinical variables might be expected after the discontinuation of dapagliflozin following this decision, there are no available data concerning this premise. Thus, in this study, we assessed the clinical impact of dapagliflozin discontinuation in patients with T1D after the withdrawal of this indication.

We performed a two-center retrospective cohort study based on the medical records of patients with T1D who received dapagliflozin as adjunctive therapy to insulin. We selected all patients with T1D with follow-up at the Department of Endocrinology, Virgen de la Victoria University Hospital (Malaga, Spain), and at Getafe University Hospital (Madrid, Spain) who discontinued dapagliflozin due to the removal of the indication of this medication for T1D from November 2021 to August 2022. Clinical and biochemical data were obtained at dapagliflozin discontinuation and the first follow-up visit after this therapeutic modification (3–6 months). Intermittently scanned continuous glucose monitoring (isCGM) metrics from FreeStyle Libre 2 were collected from libreview.com, considering a 14-day period. This study was conducted according to the principles of the Declaration of Helsinki. All participants gave their signed informed consent to participate in this study and approved the access to their personal medical information.

In total, 38 patients with T1D (46.9 ± 11 years [mean ± SD age]; 25.7 ± 10.2 months of dapagliflozin treatment before discontinuation) were analyzed. Most participants were using multiple-daily-injection therapy (n = 31, 81.6%), whereas the rest of the participants were users of continuous subcutaneous insulin infusion systems. No changes in insulin therapy (type of insulin or multiple daily injections/continuous subcutaneous insulin infusion) were performed together with dapagliflozin discontinuation. A proportion of 84.2% of patients (n = 32) were using isCGM devices as a method of glucose testing. A proportion of 60.5% of the study participants were taking dapagliflozin at high doses (10 mg).

Changes in weight, HbA_{1c}, insulin dose, and isCGM metrics from baseline (at dapagliflozin discontinuation) to the first follow-up visit following dapagliflozin discontinuation (3–6 months, 157.5 ± 50.2 days) were evaluated (Table 1). Body weight increased a mean of 2 kg (95% CI 1–3 kg) following dapagliflozin discontinuation, while the mean HbA_{1c} increase from baseline was 0.34% (95% CI 0.14–0.54%). Total daily insulin dose also was higher after dapagliflozin discontinuation (increase of 7.8%, 95% CI 3.1–12.5%). Additionally, significant changes in isCGM metrics were detected. In this regard, a mean decrease of 7.2% in time in range (TIR) was observed at the expense of an increase in time above range. Mean interstitial glucose and glucose management indicator also increased after dapagliflozin discontinuation.

Previously, a retrospective analysis based on data of 91 patients from the Dapagliflozin Evaluation in Patients With Inadequately Controlled Type 1 Diabetes 1 and 2 (DEPICT-1 and DEPICT-2) trials

[1]*Department of Endocrinology and Nutrition, Virgen de la Victoria University Hospital, Málaga, Spain*
[2]*Instituto de Investigación Biomédica de Málaga-Plataforma Bionand, Málaga, Spain*
[3]*Faculty of Medicine, University of Málaga, Málaga, Spain*
[4]*Centro de Investigación Biomédica en Red de la Fisiopatología de la Obesidad y la Nutrición, Instituto de Salud Carlos III, Madrid, Spain*
[5]*Department of Endocrinology and Nutrition, Getafe University Hospital, Madrid, Spain*

Corresponding authors: José Ignacio Martínez-Montoro, joseimartinezmontoro@gmail.com, and María José Picón-César, mjpiconcesar@gmail.com

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J.I.M.-M. and M.J.P.-C. contributed equally to this work and share first authorship.

Table 1—Changes in weight, HbA_{1c}, insulin requirements, and isCGM metrics from baseline (dapagliflozin discontinuation) to 3–6 months

	Baseline	3–6 months	*P* value
Weight (kg) (*n* = 38)	86.3 ± 17	88.3 ± 16.7	<0.001
BMI (kg/m^2) (*n* = 38)	30.8 ± 5.4	31.6 ± 5.4	<0.001
HbA_{1c} (%) (*n* = 35)	7 ± 0.7	7.3 ± 0.8	0.002
Basal insulin (IU) (*n* = 31)	31.8 ± 11.2	34.1 ± 10.2	0.003
Prandial insulin (IU) (*n* = 28)	25.7 ± 14.4	28.3 ± 16.5	0.025
TDI (IU/kg) (*n* = 28)	0.64 ± 0.25	0.69 ± 0.24	0.003
Daily scans (number) (*n* = 32)	12.2 ± 6.4	11.4 ± 7.1	0.538
Average glucose (mg/dL) (*n* = 32)	153.8 ± 21.4	162.1 ± 19.6	0.007
Glucose variability (%, CV) (*n* = 32)	33.3 ± 6.3	35.4 ± 6	0.057
TIR (%) (*n* = 32)	68.7 ± 10.1	61.6 ± 12.3	0.001
TAR (%) (*n* = 32)	27.7 ± 12.7	34.6 ± 12.9	0.002
TBR (%) (*n* = 32)	3.6 ± 5.3	3.8 ± 4.6	0.335
GMI (%) (*n* = 32)	7 ± 0.5	7.2 ± 0.5	0.003

Data are presented as mean ± SD. Paired Student *t* test was used for comparisons for those variables with a normal distribution (weight, BMI, HbA_{1c}, CV, and TIR). Wilcoxon signed-rank test was performed for those variables without a normal distribution (basal insulin, prandial insulin, TDI, daily scans, average glucose, TAR, TBR, and GMI). *P* values < 0.05 were considered significant. CV, coefficient of variation; GMI, glucose management indicator; IU, international units; TAR, time above range (>180 mg/dL); TBR, time below range (<70 mg/dL); TDI, total daily insulin dose; TIR, time in range (70–180 mg/dL).

reported adverse changes in HbA_{1c}, body weight, and insulin requirements following dapagliflozin discontinuation (3). However, the reason for dapagliflozin discontinuation was mainly related to adverse events or the completion of the scheduled treatment. Moreover, these results were obtained in a clinical trial setting, and the authors recognized that results might be influenced by the return to "real-life" conditions. Conversely, we only included patients with T1D who discontinued dapagliflozin due to the withdrawal of the indication for this population. Furthermore, our study was conducted in a real-world setting, and most participants had followed long-term therapy with dapagliflozin before its discontinuation.

Only a few studies have evaluated continuous glucose monitoring metrics in patients with T1D treated with sodium–glucose cotransporter 2 inhibitors (2). Remarkably, a reduction in TIR of approximately 7% was observed following dapagliflozin discontinuation in our population. Since the risk for the development of chronic complications associated with T1D markedly increases for each 10-percentage-points-lower TIR (4), our findings might have important clinical consequences.

This study has some limitations. First, due to its retrospective nature and the limited sample size, these findings should be cautiously interpreted. Similar to previous real-world studies (5), dapagliflozin was used at high doses in a significant number of participants, mainly because it was the only commercialized dose in Spain; therefore, different outcomes might be expected following the discontinuation of dapagliflozin in different clinical settings. Another limitation of this study was the lack of a control group. Further, the effect of dapagliflozin discontinuation and its negative impact on metabolic control were assessed in the very short term.

In conclusion, in a cohort of patients with T1D, dapagliflozin discontinuation led to an overall deterioration of glycemic control, significant weight gain, and increased insulin requirements. Further research is needed to evaluate long-term clinical consequences of the discontinuation of dapagliflozin in patients with T1D after the removal of this indication.

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