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TRABAJO DE FIN DE GRADO EN MEDICINA

Retrospective observational study on the effect of the use of SGLT2 inhibitors in the treatment of Type I Diabetes Mellitus

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1. ABSTRACT

I. ABSTRACT IN ENGLISH

Type I diabetes is one of the most relevant metabolic diseases today, both worldwide and in our environment. Its treatment has historically been based on the administration of insulin and, although this is still the case, new alternatives are transforming or adding to this treatment. This study aims to compare the effects of treatment with multiple insulin injections plus Dapagliflozin (SGLT2 inhibitor) with those of treatment with a Continuous Insulin Infusion Pump. Such effects include their effectiveness and efficiency in lowering HbA1c levels, as well as promoting weight loss and glycemic control (HbA1c<7%). For this purpose, data in this regard were extracted from patients' medical records, and subjected to statistical analysis. The costs of each treatment were also calculated. In addition, the possible adverse effects were observed and collected. It was concluded that treatment with Dapagliflozin was more efficient and perhaps more effective in lowering HbA1c. It was also the only treatment shown to contribute significantly to weight loss. On the other hand, no significant adverse effects were reported in either group. These results could be of particular relevance after the withdrawal of the indication of Dapagliflozin for the treatment of IMD.

KEYWORDS: Dapagliflozin, SGLT2 inhibitor, T1D, T1DM, Type 1 diabetes mellitus, Continuous Insulin Infusion Pump, CIIP, HbA1c

II. ABSTRACT IN SPANISH

La Diabetes tipo I es una de las enfermedades metabólicas más relevantes a día de hoy, tanto a nivel mundial como en nuestro medio. Su tratamiento ha estado históricamente basado en la administración de insulina y, aunque sigue siendo así, nuevas alternativas están transformando o sumándose a dicho tratamiento. Este estudio pretende comparar los efectos del tratamiento mediante múltiples inyecciones de insulina sumadas a Dapagliflozina (ISGLT2) con los del tratamiento con Bomba de Infusión Continua de Insulina. Dichos efectos incluyen su efectividad y eficiencia a la hora de disminuir los niveles de HbA1c, así como de promover la pérdida de peso y el

control glucémico (HbA1c<7%). Para ello, se extrajeron los datos a este respecto de las historias clínicas de los pacientes, y se sometieron a un análisis estadístico. También se calcularon los costes de cada tratamiento. Además, se recogieron los posibles efectos adversos observados. Se concluyó que el tratamiento con Dapagliflozina fue más eficiente y puede que más efectivo a la hora de disminuir la HbA1c. También fue el único tratamiento que mostró contribuir de forma significativa a la pérdida de peso. Por otro lado, no se contabilizaron efectos adversos significativos en ninguno de los grupos. Estos resultados podrían tener especial relevancia tras la retirada de la indicación de la Dapagliflozina para el tratamiento de la DMI.

PALABRAS CLAVE: dapagliflozina, ISGLT2, DMI, diabetes mellitus tipo 1, bomba de infusión continua subcutánea de insulina, ICSI, HbA1c

2. INTRODUCTION

Type I Diabetes is currently one of the most relevant endocrine diseases all around the world. Its prevalence in Spain is estimated to be around 0.2%, which means that 90,000 people are affected by it only in our country[9]. In regard to its treatment, Insulin replacement has been and still remains its cornerstone. The aim of Insulin administration is to maintain blood glucose levels in the normal physiological range, as much as possible, while also permitting certain flexibility when it comes to mealtimes and activity levels. These treatment regiments classically incorporated different components: Basal insulin, which prevents gluconeogenesis and ketogenesis during the prepandial state; mealtime insulin (normally rapid or ultra-rapid acting), which is intended to cover carbohydrate and other macronutrients intake; and correction insulin, in case hyper-glycemia occurs. These different elements are usually self-injected subcutaneously by patients themselves, via Multiple Daily Injections.[6] [7]

However, newer options are now available to patients, one of them being continuous subcutaneous insulin infusion via a pump of a rapid-acting insulin analog. Insulin pumps simulate natural insulin pulses after meals, according to the patient's requirements.[12]

These devices offer, among other advantages, an improvement in metabolic control and a reduction in hypoglycemia[6][7] and, in some cases, an increase in the perception of quality of life. In addition, they can also allow a reduction in insulin dosage[4]. However, they require a great deal of

involvement and collaboration on the patient's side[8], in addition to entailing high health care costs[6][7].

On the other hand, and with insulin therapy still being the main treatment, other drugs are being included in recent times for the treatment of IMD. This is the case of Type 2 Sodium-Glucose Cotransporter Inhibitors, which work by inducing glucosuria, as they inhibit glucose reabsorption in the proximal tubule of the nephron[1][2][3][4][6][7], and whose efficacy in the treatment of Type 2 Diabetes is more than proven[14]. Not only do they improve glycemic control without producing a considerable increase in hypoglycemia, but also have a proven cardio- and nephroprotective effect and increase weight loss[13][14][15]. In 2019, one of them, Dapaglifozin, was approved by the European Medicines Agency for its use in conjunction with insulin in the treatment of patients with Type 1 Diabetes who had a BMI greater than or equal to 27 kg/m2.[16]

The latest studies show benefits of the addition of Dapaglifozin to insulin therapy, providing better glycemic control, as well as lower incidence of cardiovascular disease, reduction of body weight and blood pressure[4][15]. A potential adverse effect could be the appearance of euglycemic ketoacidosis, which is more difficult for the patient to detect than the usual ketoacidosis, due to normal glucose levels. This possibility could require closer monitoring.[15]

Subsequently, EU and UK medicines regulators required the drug to include the black triangle symbol on the packaging, meaning that additional monitoring would be needed when prescribing this drug for Type 1 Diabetes. In response to this requirement, the company decided to voluntarily withdraw the indication of Dapagliflozin for the treatment of Type I Diabetes[10] [11][17], claiming that the changes "might cause confusion among physicians treating patients with type 2 diabetes, heart failure with reduced ejection fraction, or chronic kidney disease." They also made some slightly confusing statements, as they, on the one hand, pointed out that a potential adverse effect of Dapagliflozin in the treatment of Type I Diabetes could be the appearance of euglycemic ketoacidosis and, on the other hand, argued that the withdrawal was "not due to any safety concern" with the drug "in any indication, including type 1 diabetes". [18]

Some sources suggest that the main reason for the removal of the indication could be a conflict of interest of a commercial nature[10] [11]. Despite the withdrawal of the indication, some patients with Type I Diabetes are still being treated with Dapagliflozin.

3. JUSTIFICATION

Due to the recent controversies in using SGLT2 inhibitors in type 1 diabetes and the fact that many patients are still being treated with Dapagliflozin, it is reasonable to analyse the benefits and drawbacks of their use in clinical practice. Moreover, it is relevant to compare this strategy with the alternative of switching patients to a Continuous Insulin Infusion Pump (CIIP) in order to improve their metabolic control, and to analyse if there are differences between the potential adverse effects.

4. HYPOTHESIS

Treatment with subcutaneous insulin in a basal bolus regimen combined with the SGLT-2 (Sodium-Glucose Transporter 2) inhibitor Dapagliflozin is more effective and efficient than treatment with a continuous insulin infusion pump in terms of glycemic control, without increasing the frequency of serious adverse effects.

5. OBJECTIVES

I. Primary objective

The main goal of this study is to evaluate the effect of the SGLT2 cotransporter inhibitor Dapagliflozin in combination with Multiple Insulin Doses (MID) on the levels of HbA1c, compared to treatment with CIIP, in patients with type 1 Diabetes Mellitus.

II. Secondary objectives

- To quantify the percentage of patients that achieved glycemic control (HbA1c < 7%) in each group.
- To evaluate the effect of each treatment in the body mass of patients.
- To quantify the incidence of episodes of euglycemic ketoacidosis.
- To quantify the incidence of other adverse effects that led to treatment discontinuation, such as severe candida infection.
- To quantify differences between the costs of both treatments, evaluating each treatment's efficiency.

6. MATERIALS AND METHODS

The study is observational and retrospective, limited to the years 2020, 2021 and 2022. It studied and compared patients with Type I diabetes at the *Hospital General Universitario de Alicante* who, during the observation period, modified their treatment with subcutaneous insulin injections. Group 1 consisted of patients who added one daily dose of Dapagliflozin 10 mg (5 mg Dapagliflozin was not available in Spain) to the bolus-basal therapy. On the other hand, Group 2 consisted of patients who changed the injections for a CIIP. The decision to add an SGLT2 inhibitor to MID (Multiple Isulin Dosis) or to switch the treatment to CIIP depended on the facultative in charge of the patient. Most of the patients with MID + SGLT2-I were treated by the same staff and most of the patients with CIIP were treated by another unique staff.

To obtain the data, the medical records of all patients who met the inclusion criteria and did not meet any exclusion criteria were reviewed.

I. Inclusion Criteria

- Being diagnosed with type I diabetes.
- HGUA patients recruited during the observation period.

- Having changed from bolus-basal insulin therapy to CIIP or addition of SGLT-2 Inhibitor to basal bolus therapy.
- Availability of at least one previous HbA1c value close to the start date of the new treatment (maximum 3 months before).
- Availability of at least one control HbA1c value between 6 and 12 months after the start of the new treatment.

II. Exclusion Criteria

- Patients combining CIIP and Dapagliflozin.
- Patients who did not meet all of the inclusion criteria.

III. Demographic and clinical characteristics of the patients in the two groups

GROUP	1	2	
TREATMENT	MID + DAPAGLIFLOZIN 10mg	CIIP	
TOTAL Nº OF PATIENTS	30	20	
Nº OF WOMEN	12	14	Pv: 0,0475 SS
Nº OF MEN	18	6	
AVERAGE AGE (years)	47,0	41,1	Pv: 0,1712 NSS
AVERAGE AGE AT DIAGNOSIS (years)	15,5	24,1	Pv: 0,0854 NSS
AVERAGE TIME OF EVOLUTION (years)	25,55	22,92	Pv: 0,4904 NSS
AVERAGE HbA1c AT DIAGNOSIS	7,973	7,56	Pv: 0,0870 NSS

Table 1. – Demographic and clinical characteristics of the two of the study.
SS: Statistically significant
NSS: Non Statistically significant
Pv: Pvalue

Pv lower than 0,05 confer Statistical Significance (Confidence Interval of 95%)

Note that the Pvalues mentioned above show no significant differences between the two groups, except for the proportion of women and men.

IV. Variables used in the study

i. Explanatory variables

- Addition of SGLT2 inhibitor to bolus-basal insulin therapy (Group 1).
- Change from bolus-basal insulin to CIIP (Group 2).

ii. Result variables

- Changes in HbA1c
- Changes in body mass
- Percentage of patients that achieved glycemic control (HbA1c < 7%) in each group.
- Recorded episodes of euglycemic ketoacidosis.
- Recorded episodes of other adverse effects leading to discontinuation of Dapagliflozin, such as yeast infections.
- Costs of treatment Insulin + Dapagliflozin
- Costs of treatment with CIIP

iii. Demographic variables

- Age of debut
- Sex
- Time of evolution of diabetes

Once the data were obtained, they were analysed statistically. In each group, it was checked whether there were significant differences in HbA1c levels by comparing the baseline value (prior to the change in treatment) with the value in the control analysis between 6 and 12 months. In addition, we also checked whether there were significant differences between the two groups in terms of the variation in HbA1c

values between the two analyses. In cases where there were several analytical controls between 6 and 12 months, the lowest HbA1c value was chosen for both groups.

The weight values of the patients at the beginning of the treatment and at a control at 6-18 months were also recorded. Subsequently, they were compared statistically in each group to see if there were significant differences between the weight at the start of treatment and the weight at the time of the control. Patients who got pregnant were excluded. The percentage of patients who achieved glycemic control in each group was calculated too, as well as whether there were significant differences in this respect.

Episodes of hypoglycemia, hyperglycemic and euglycemic ketoacidosis leading to hospitalization, and candidiasis in the genitourinary tract leading to discontinuation of treatment were also carefully sought in both groups. Given the small number of episodes of this type, it was not necessary to apply a statistical analysis.

As for the cost of treatment for both groups, an approximate price per year was calculated. In Group 1, the cost of Dapagliflozin was added to the cost of subcutaneous insulin injections and that of the Continuous Glucose Monitoring System, that has a longevity of 14 days. An average patient weight of 70 kg, a total insulin dose of 0.5 U/kg/day (60% rapid and 40% slow) and a Dapagliflozin dose of 5 mg/day were used. In Group 2, the cost of the device (which includes the monitoring system) was added to the cost of the insulin used. An average weight per patient of 70 kg and a total insulin dose of 0.5 U/kg/day (100% rapid insulin) was considered.

7. STATISTICS

During the study we analysed both continuous quantitative variables (HbA1c levels and patient weight) and dichotomous qualitative variables (subjects who did reach control and subjects who did not reach control).

In the case of the Comparison between baseline HbA1c values (before the change in treatment) and those obtained in the control 6-12 months after the change in treatment, the groups to be analysed are dependent. To determine whether the values conformed to a normal distribution, the D'Agostino and Pearsons test was used. Group 1 passed the normality test, and it was also verified that there was homoscedasticity, so a paired t-test was used in this group. The paired t-test compares the means of two matched groups, assuming that the distribution of the before-after differences follows a Gaussian distribution.

Group 2, on the other hand, did not pass the normality test, so the Wilcoxon test was applied. The Wilcoxon test is a nonparametric test that compares two paired groups.

In the case of the Comparison of the decreases in the HbA1c values of Group 1 with those of Group 2, said groups were independent. When using the D'Agostino and Pearsons test, it was found that the values did not conform to a normal distribution, so the Mann-Whitney test, a non parametric test that compares the two unmatched groups, was used.

For the Comparison between baseline weight values (before the change in treatment) and those obtained in the control 6-18 months after the change in treatment, the groups to be analysed were, again, dependent. Again using the D'Agostino and Pearsons tests, group 1 conformed to a normal distribution, while group 2 did not. Therefore, the Paired t-test and the Wilcoxon test were used, respectively.

Finally, when comparing the number of individuals who achieved glycemic control (HbA1c < 7%) in Group 1 vs. Group 2, a contingency table was prepared and a Fisher's Exact Test was applied.

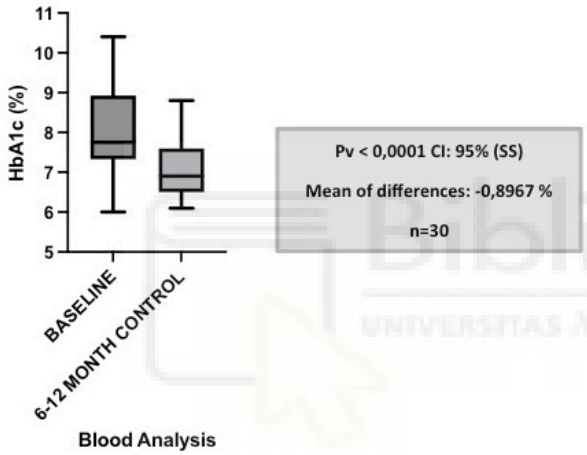
Differences were considered to be significant with a Pvalue<0.05 and a 95% confidence interval.

8. RESULTS

I. Comparison between baseline HbA1c values and 6-12 month control values

i. Group 1: Dapagliflozin 10 mg (1 tablet/day) + MID

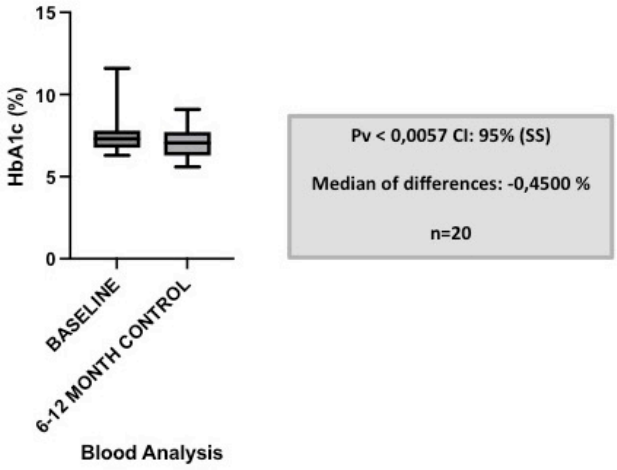
The calculated Pvalue was <0,0001. Therefore, it was determined that there were significant differences between the baseline HbA1c values and those recorded at 6-12 months.



Graph 1: Comparison between baseline HbA1c values and 6-12 month control values in Group 1.
SS: Statistically Significant
Pv: Pvalue
CI: Confidence Interval
n: number of patients

ii. Group 2: CIIP

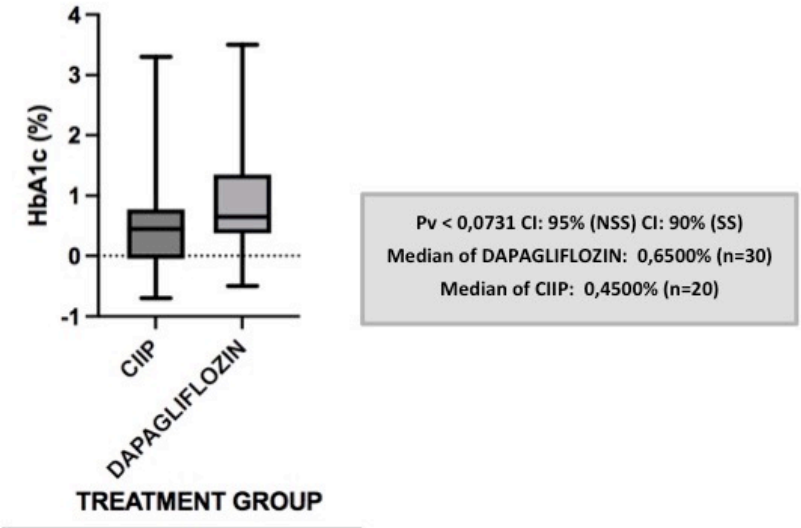
The calculated Pvalue was 0.0057. Therefore, it was determined that there were significant differences between the baseline HbA1c values and those recorded at 6-12 months.



Graph 2: Comparison between baseline HbA1c values and 6-12 month control values in Group 2.
SS: Statistically Significant
Pv: Pvalue
CI: Confidence Interval
n: number of patients

II. Comparisson between the decreases in Group 1 and Group 2

The calculated Pvalue turned out to be 0.0731. Therefore, it was determined that there were no significant differences in the decreases of HbA1c in both groups with a confidence interval of 95%. However, since the Pvalue would have to be less than 0.1, a condition that would be met in this case. It could be determined that there were significant differences between the decreases in HbA1c in both groups with a 90% confidence interval.

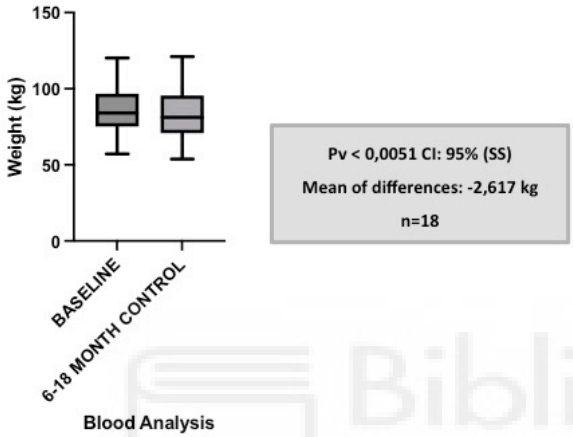


Graph 3: HbA1c reduction comparisson between groups.
SS: Statistically Significant
NSS: Non Statistically Significant
Pv: Pvalue
CI: Confidence Interval
n: number of patients

III. Comparison between baseline weight values and 6-18 month control values

i. Group 1: Dapagliflozin 10 mg (1 tablet/day) + MID

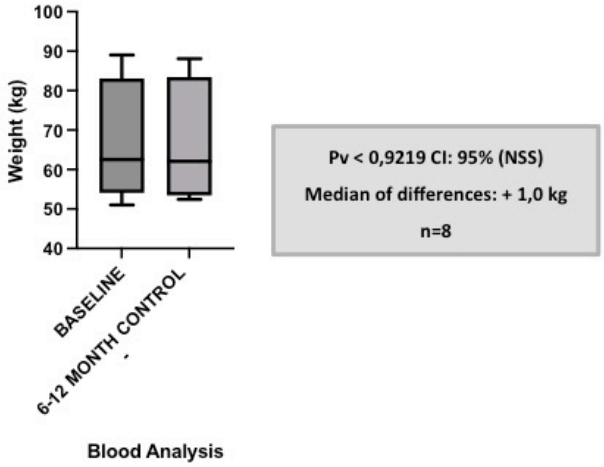
The calculated Pvalue was 0,0051. Therefore, it was determined that there were significant differences between the baseline weight values and those recorded at 6-18 months.



Graph 4: Baseline vs. Control Weight in Group 1
SS: Statistically Significant
Pv: Pvalue
CI: Confidence Interval
n: number of patients

ii. Group 2: CIIP

The calculated Pvalue was 0,9219. Therefore, it was determined that there were no significant differences between the baseline weight values and those recorded at 6-18 months.



Graph 5: Baseline vs. Control Weight in Group 2.
NSS: Non Statistically Significant
Pv: Pvalue
CI: Confidence Interval
n: number of patients

IV. Comparison between the amount of patients that achieved glycemic control (HbA1c < 7%) in each group after 6-12 months of treatment.

GROUP	Number of subjects with HbA1c < 7%	Number of subjects with HbA1c >/= 7%
DAPAGLIFLOZIN + MID (n=30)	17	13
CIIP (n=20)	9	11

Table 2 – Control achievement in each group.

The calculated Pvalue was 0,9219. Therefore, it was determined that there were no statistically significant differences between the amount of patients that achieved control in 6-12 months.

As for the adverse effects of Dapagliflozin treatment, there were no episodes of ketoacidosis (euglycemic or hyperglycemic) after its initiation. Only one of the patients in Group 1 had ketonuria of 5mg/dL on one

occasion; another patient had ketonuria of more than two crosses in the context of an intercurrent infection, which resolved when the infectious process resolved.

Severe hypoglycemia was also recorded in one of the patients; that patient had presented repeated severe hypoglycemias prior to the introduction of Dapagliflozin. Finally, one patient presented with candidiasis and one patient with candidiasis balanitis, which resolved with antifungal treatment without requiring discontinuation of treatment. In the CIIP group, one patient presented candidiasis.

V. Cost of the treatments

i. Treatment 1: Dapagliflozin + MID

TREATMENT 1 Dapagliflozin + MID
70 kg · 0.5 U/kg/day = 45 U/day
Slow insulin price: 0.0734€/U
Rapid insulin price: 0.0288€/U
45U/day · 0.4 = 18 U/day of slow insulin
45U/day · 0.6 = 27 U/day of rapid insulin
18 U/day · 0.0734€/U = 1.3212€/day of slow insulin
27 U/day · 0.0288€/U = 0.7776€/day of rapid insulin
Total insulin/day = 2.0988 €
Total insulin/year= 2.0988 €/day · 365 days/year = 766.062 €
Estimated annual price of Dapagliflozin = 729.35€.
Estimated annual price of Continuous Glucose Monitoring system: 59,91€/unit · 27 U/year = 1617,57 €/year [22]
Estimated total annual price of treatment 1 **3112,69€.**

Table 3 – Estimated total annual price of treatment 1

ii. Treatment 2: CIIP

TREATMENT 2 CIIP
70 kg · 0.5 U/kg/day = 45 U/day
Rapid insulin price: 0.0288€/U
45 U/day · 0.0288€/U = 1.296€/day (total insulin)
Total Insulin/year = 1,296/day · 365 days/year = 473.04€/year
Monthly cost of the pump: 506€.
Annual cost of the pump: 6072€.
Estimated total annual price of treatment 2 **6545.04€/year**

Table 4 – Estimated total annual price of treatment 2

As it is clear by the calculations above, the cost of treatment 2 easily doubles that of treatment 1. This would imply that, even if we consider a non-statistically significant effectiveness, the efficiency of adding Dapagliflozin to the treatment with subcutaneous insulin injections would be higher than that of changing these injections for a CIIP.

9. DISCUSSION

Comparison between baseline HbA1c values and those obtained after 6-12 months in the Dapagliflozin group revealed a significant decrease in these values during the study period. With respect to the adverse effects of treatment, the lack of serious events (understood as the need for admission or suspension of treatment due to the episode) made a statistical analysis of these unnecessary.

Regarding the comparison between baseline HbA1c values and those obtained after 6-12 months in the CIIP group, a statistically significant decrease was found as well during the study period. It is interesting to point out that some of the patients in this group wanted to improve their glycemic control due to gestational desire. In 3 of the cases, the patients achieved pregnancy after the introduction of the new treatment. The tendency to hyperglycemia during gestation could potentially influence the results of the study. Therefore, in view of future studies, the exclusion of these patients could be proposed.

In regards to the comparison of HbA1c decreases between Group 1 and Group 2, this difference was not statistically significant for a 95% confidence interval, but it would be for a 90% confidence interval. The lack of statistical significance in the first case could be related to the great difficulty in obtaining homogeneous analytical data, to the point of having to exclude patients due to the lack of HbA1c data corresponding to the periods studied, thus reducing the available sample size.

It is important to comment on the peculiarities of the patients who are candidates and/or suitable for each treatment. In the case of CIIP, due to the great importance of adequate patient training for its correct use, the selection of responsible and highly involved patients, willing to go through proper training regarding the device, is crucial. In addition, they must be capable individuals, with a higher degree of ability and understanding of their disease. In fact, in the clinical records of some of these patients, "deficiencies in the knowledge of the use of the pump" which could lead to suboptimal use, not obtaining the desired glycemic control[8], were repeatedly noted.

On the other hand, a type of patient who could benefit from this treatment would be those who have a genessic desire and/or pregnancy. CIIP is not contraindicated in these cases, and could provide the increase in glycemic control necessary for a pregnancy with lower risks [19]. In addition, these patients would not be candidates for treatment with Dapagliflozin, since it is contraindicated during pregnancy and lactation. [20]

As for the advantages of the treatment with Dapagliflozin, beyond glycemic control, previous studies have demonstrated cardioprotective and nephroprotective effects, as well as a decrease in blood pressure and body weight[4] [16] (the latest being observed in Group 1). We must bear in mind that Type I Diabetes is a major cardiovascular risk factor and for the development of renal failure, as is high blood pressure. Overweight, on the other hand, is by itself a cardiovascular risk factor[21]. Therefore, it would be logical to infer that those patients who, in addition to type 1 DM, present pathology of the aforementioned types, would obtain an added benefit from the use of Dapagliflozin. On the other hand, the use of

Dapagliflozin does not require as exhaustive patient education as the pump, so it could be used in less proactive and less trained patients.

In terms of efficiency, Group 1 treatment was shown to be clearly superior, offering better or at least similar results (with 90 and 95% CI, respectively) with half the cost per patient. To illustrate this difference, the patients in Group 2 without gestational desire or gestation (a total of 16), generated a total expenditure of approximately 104,720€. If these patients, who could be eligible for treatment with Dapagliflozin, had followed the treatment of group 1, they would have generated an expense of approximately € 49,803 which would have resulted in a saving of € 54,917.

When looking for potential adverse effects, the ones quantified were punctual and mild, except for a severe hypoglycemia in a patient with a previous history of hypoglycemia the Dapagliflozin group. Note that previous studies indicate that Dapagliflozin would not produce an increase in the number of hypoglycemias[1].

We should also comment on what is perhaps the most controversial point of this work: the reason for the withdrawal of the indication for Dapagliflozin in patients with Type I Diabetes. This is not a simple question, since not even AstraZeneca themselves were clear in explaining the withdrawal. On the one hand, in its press release, they stated the following: "Diabetic ketoacidosis (DKA) is a known side effect of dapagliflozin. In T1DM studies with dapagliflozin, DKA was reported with common frequency (occurring in at least 1 per 100 patients)". However, in the same statement, they assured that the withdrawal "was not due to any safety concern" with the drug "in any indication, including type I diabetes." The pharmaceutical company stated, in turn, that the decision "follows discussions regarding product information changes needed post-approval for dapagliflozin 5 mg specific to type I diabetes which might cause confusion among physicians treating patients with type 2 diabetes, chronic heart failure with reduced ejection fraction, or CKD". The changes to the drug information would presumably relate to the need to include a black triangle on the packaging as a safety warning for patients with type 1 DM, who would require routine monitoring when using the drug. [5] [10] [11] [16] [17] [18]

From the data stated above, we could infer that at least part of the decision to withdraw the indication had a commercial nature, considering that the warning could cause alarm among physicians and patients who were already using Dapagliflozin previously. Since the number of patients already using the indication (type II diabetics, cardiac patients or patients with renal pathology without type I diabetes) would be higher than that of patients with type I DM, the pharmaceutical company may have considered it risky to lose some of the former by extending the indication to the latter.

10. STUDY LIMITATIONS

One of the major limitations of the study was to find blood analyses of the patients that were adapted to the periods studied. At the beginning, the study intended to establish a more constant follow-up, from 3 months to 3 months approximately, but it was impossible to find blood analyses performed with such frequency in a large number of the subjects. The same challenge was also encountered regarding the weight analysis. This also led to discarding secondary objectives that were initially proposed, such as the analysis of changes over time in achieving glycemic control or changes in blood pressure.

We should also take into consideration variables that can lead to changes in the patients' glycemic control, and which are more common in one group than in another. For example, one of the reasons why patients in Group 2 opted to change their usual treatment to the pump system was that they had a desire for pregnancy, since good glycemic control is key in pregnancy. In contrast, Dapagliflozin is contraindicated during pregnancy, and there were no patients with these characteristics in Group 1.

Finally, regarding possible adverse effects, the time of observation and the quality of the records would also be a limitation, since the benefits could be overestimated over the risks not recorded in the clinical records.

11. CONCLUSIONS

Both adding one daily dose of Dapagliflozin 10 mg to subcutaneous bolus insulin therapy and swithching to a CIIP showed significant efficacy in lowering HbA1c in type 1 diabetic patients in our study. The efficacy of adding Dapagliflozin was equal or superior than that of switching to a CIIP, depending on the confidence interval, whilst the efficiency was clearly superior. The percentage of patients that achieved glycemic control was not significantly different between groups. Weight loss during the study was statistically significant only in the Dapagliflozin group. There was not a significant amount of notable adverse effects, including euglycemic ketoacidosis, in neither of the groups.

Given this results, it may be appropriate to reconsider re-including the indication of Dapagliflozin for the treatment of IMD.

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