Abstract

Aim: To verify the efficacy of CSII treatment and determine patient’s clinical features that could have influenced the posterior metabolic control.

Methods: 37 patients; 21 males and 16 females, mean age of 36.2 ± 9.4 years. Mean duration of diabetes prior to CSII of 16.2 ± 7.4 years and previous year mean A\textsubscript{1c} of 8.1 ± 0.9%. Diabetic complications: 50% retinopathy, 19% nephropathy, and 11.4% neuropathy. Indications for CSII: poor metabolic control (33.3%), patient request (27.8%), frequent hypoglycaemia (22.2%), glycaemic variability (13.9%) and other (2.8%).

Results: Starting A\textsubscript{1c} was lowered significantly in the first year of CSII –0.71 ± 0.58% (p <0.001) and stable –0.9 ± 0.54% (p <0.001) after 36 months. Basal insulin requirements decreased and subsequently remained stable (start: 0.29 ± 0.08 U/kg/d; after 36 months: 0.32 ± 0.14 U/kg/d). The greatest reduction in A\textsubscript{1c} was found in patients with higher baseline A\textsubscript{1c} and longer duration of diabetes.

Conclusions: CSII resulted in a steady improvement in glycaemic control and reduction in insulin requirements. It could be considered a predictor factor of treatment effect.

Keywords: type 1 diabetes mellitus, insulin pump, multiple daily insulin injections, glycosylated haemoglobin.

Resumen

Objetivo: Verificar la efectividad del tratamiento y determinar las características clínicas de los pacientes que han podido influir en el control metabólico posterior.

Materiales y métodos: Se estudió a 37 pacientes (21 varones y 16 mujeres), con una media de edad de 36,2 ± 9,4 años. El tiempo de evolución de la diabetes previa a la infusión subcutánea continua de insulina (ISCI) fue de 16,2 ± 7,4 años. Las complicaciones angiopáticas fueron la retinopatía (50%), la nefropatía (19%) y la neuropatía (11,4%). Los motivos de indicación de ISCI fueron los siguientes: mal control (33,3%), petición propia (27,8%), hipoglucemias (22,2%), variabilidad glucémica (13,9%) y otros (2,7%).

Resultados: Se observó un descenso de la hemoglobina glucosilada (HbA\textsubscript{1c}) a los 12 meses de –0,71 ± 0,58% (p <0,001), que se mantuvo a los 36 meses en valores de –0,9 ± 0,54% (p <0,001). Los requerimientos de insulina basal disminuyeron y posteriormente se mantuvieron estables (inicio: 0,29 ± 0,08 U/kg/día; 36 meses: 0,32 ± 0,14 U/kg/día). Se apreció una ganancia de peso en los pacientes de 2,7 ± 4,8 kg a los 3 años con ISCI. Los participantes con una mayor HbA\textsubscript{1c} basal y un tiempo más largo de evolución de la diabetes presentaron un descenso superior de la HbA\textsubscript{1c} con ISCI.

Conclusiones: Se constató una mejora mantenida del control glucémico y un descenso de las necesidades de insulina basal. El mayor descenso de la HbA\textsubscript{1c} se obtuvo en los pacientes con una mayor evolución de la diabetes y un peor control, que eran factores pronóstico de una mejor respuesta a esta terapia.

Palabras clave: diabetes mellitus tipo 1, bomba de insulina, dosis múltiples de insulina, hemoglobina glucosilada.
patients screened with T1D. In Spain, the implantation of CSII is estimated in 0.79% of the persons with T1D according to the data obtained by the Grupo de Trabajo de Nuevas Tecnologías de la Sociedad Española de Diabetes (SED). (Group of Work of New Technologies of the Spanish Diabetes Society).\(^1\) Pickup et al. made a revision of the studies that compared the use of therapeutic regimes of MDI based on long- and fast-acting insulin analogues versus the CSII and concluded that the long-acting insulin analogues have not yet replaced the treatment with CSII in patients with T1D and that at present the CSII constitutes the best therapeutic option for some of these patients.\(^2\) Zietlger et al. performed a parallel study of 2 years of follow-up, in which they compared the treatment with CSII in which regular insulin was used versus MDI with regular insulin/NPH, without observing relevant statistically differences in the glycemic control between both groups, with a glycosylated hemoglobin (HbA\(_1c\)) of 8.7 versus 8.4%, respectively.\(^3\)

We have done this study with the aim of analyzing the results of the treatment with CSII in our environment, and in this way to verify the efficacy of this therapeutic modality during the follow-up and to determine the clinical characteristics of the patients who might have influenced in the later metabolic control. Actually, the characteristics of patients that could condition a better response to the treatment with CSII, are not well determined. Therefore, this study has the aim of determining the clinical characteristics of the patients that might have an influence in the later metabolic control.

**Material and methods**

For the performance of this study, we have included all the patients (47 diabetic type 1 patients) who underwent treatment with CSII in the Endocrinology Service of the Hospital of Navarra from 2005 to 2008. The exclusion criteria have been the starting of the treatment in another site (n= 4) and a duration of the treatment with CSII under 6 months (n= 6). Finally, the data of 37 patients have been analyzed.

The patients were screened to receive treatment with CSII following the indication criteria recommended by the SED.\(^4\) Considering the relevance of the therapeutic compliance and the therapeutic education as efficient strategy for its obtaining,\(^5\) the candidate patients completed a program of diabetology education settled by the team of educator nurses of the Endocrinology Service of the Hospital of Navarra. Such program was carried out individually with an approximate duration of 5-6 sessions. The patients received daily classes of 1 hour of length about the knowledge related to the control of the diabetes: diet (diet per portions, ketosis diet), acute complications (hyperglycemia, hypoglycemia, ketonemia), modification of the treatment, physical exercise, trips and special situations (short length disconnection, extended, during weekend). Likewise, they got knowledge related to the handling and the terminology of the CSII: programming of the watch, programming and modification of the basal infusion, stop and restarting of the pump, recognition of the alarms and actions before them, preparation and placement of the cartridge and the catheter and maintenance of the CSII. Then, the patients received the pump and a simulation period of 2 days was carried out. Once this process came to an end, the infuser was placed in the patients and the first change of catheter was done at the nursing consultation. The first 2 days the intake was reduced to 3 main meals, and the patients received a unique basal index in order to be able to perform the necessary adjustments.

The estimation of the total dose in our patients was determined substracting 20% to the total of accumulated doses with T1D. The 50% of the obtained total determines the basal dose, and the bolus the outstanding 50%. The assignment of the insulin pump was done considering the cession. Moreover, the fungible materials, the catheters, the reservoir and strips of ketonic bodies were administered to the patients.

Finally, 37 patients were included in the study, 21 men and 16 women, who had a mean treatment time with CSII of 31.7 ± 19.3 months. As basal characteristics, the patients showed a mean age of 36.2 ± 9.4 years and an initial body mass index (BMI) of 24.9 ± 3.6. The 27.3% were smokers. When starting with the CSII, they had a mean evolution of the diabetes of 16.2 ± 7.4 years and 56.8% showed at least a complication: retinopathy (50%), nephropathy (19%) and neuropathy (11.4%). The metabolic control level of the previous year was estimated by means of the estimation of the mean value of the HbA\(_1c\), which was of 8.1 ± 0.9%. The reason of the main indication of the CSII was the inadequate metabolic control (33%) and the rest of the indications were the following ones: own request (27.8%), frequent hypoglycemias (22.2%), wide glycemic variability (13.9%) and

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Combination of several indications could be offered (table 1). The evolution analysis of the glycemic control ($\text{HbA}_1c$), the weight and the insulin requirements were performed comparing the mean values at the starting and after 12, 24 and 36 months of the treatment. The Student $t$ test was used in the study of the changes in the quantitative variables for paired-off samples. The correlation coefficients were estimated. The multiple regressions (stepwise) were used in order to determine the possible variables associated to the improvement of the $\text{HbA}_1c$ (gender, age, mean of $\text{HbA}_1c$ of the previous year, evolution time and BMI). The confidence intervals (CI) were estimated of 95%. A value of $p < 0.05$ was considered a priori as statistically relevant.

### Results

A relevant decrease was observed in the mean of the basal $\text{HbA}_1c$ of $-0.71 \pm 0.58\%$ ($p < 0.001$) after 12 months of treatment. This improvement of the glycemic control was kept, and reductions of the $\text{HbA}_1c$ were observed of $-0.9 \pm 0.72\%$ ($p < 0.001$) after 24 months compared to the basal hemoglobin and of $-0.9 \pm 0.54\%$ ($p < 0.001$) after 36 months.

From the starting of the CSII, the requirements of the basal insulin were kept stable during the follow-up: at the beginning they were of $0.44 \pm 0.16$ U/kg/day, after 12 months of $0.32 \pm 0.11$ U/kg/day, after 24 months of $0.33 \pm 0.13$ U/kg/day and after 36 of $0.32 \pm 0.14$ U/kg/day (table 2). These requirements were significantly lower than the ones observed at the beginning of the therapy ($0.44$ versus $0.29$ U/kg/day; $p < 0.001$). The dose of insulin administered in bolus form could not be assessed given that many patients did not register it exhaustively.

As regards to the weight after 3 years of treatment, the patients increased $2.7 \pm 4.8$ kg. The highest weight gain ($1.6$ kg; CI of $95\%$: $0.45-2.75$; $p = 0.008$) took place after 6 months and was not correlated to the change of $\text{HbA}_1c$ (coefficient of Pearson $<0.27$; $p = 0.14$).

The participants with worse glycemic control at the beginning of the CSII, or in other words, with higher basal $\text{HbA}_1c$, and a longer diabetes evolution time, showed a higher decrease of $\text{HbA}_1c$ with this treatment modality. Thus, a reduction of $0.3\%$ was observed for each increase of $1\%$ in the mean $\text{HbA}_1c$ of the previous year (CI of $95\%$: $0.04-0.58$) at the beginning of the treatment with CSII. Likewise, for each additional year of the diabetes evolution, before the beginning of the treatment, a reduction was observed in the $\text{HbA}_1c$ of $0.04\%$ (CI of $95\%$: $0.01-0.08$).

The treatment with CSII was not interrupted or abandoned in any case. Five patients showed ketoacidosis due in part to a failure of the catheter and the non adminin-

### Table 1. Basal characteristics of the patients with T1D treated with CSII

<table>
<thead>
<tr>
<th>Basal characteristics</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>37 (21 men, 16 women)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>36.2 ± 9.4</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>27.3</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>24.9 ± 3.6</td>
</tr>
<tr>
<td>Time of the diabetes evolution (years)</td>
<td>16.2 ± 7.4</td>
</tr>
<tr>
<td>Time of follow-up (years)</td>
<td>31.7 ± 19.3</td>
</tr>
<tr>
<td>$\text{HbA}_1c$, during the year pre-CSII (%)</td>
<td>8.1 ± 0.9</td>
</tr>
<tr>
<td>Basal dose of insulin (U/kg/day)</td>
<td>0.29 ± 0.8</td>
</tr>
<tr>
<td>Reason for the indication of CSII</td>
<td>Inadequate metabolic control (33%), own request (27.6%), frequent hypoglycemies (22.2%), wide glycemic variability (13.9%), others (2.7%)</td>
</tr>
<tr>
<td>Complications</td>
<td>Retinopathy (50%), nephropathy (19%), neuropathy (11.4)</td>
</tr>
</tbody>
</table>

Data expressed as mean ± standard deviation, unless the contrary is specified. BMI: body mass index; CSII: continuous subcutaneous insulin infusion.

### Table 2. Evolutive changes regarding to the basal values of $\text{HbA}_1c$ and requirements of the basal insulin

<table>
<thead>
<tr>
<th>Evolutive changes as regards to the basal values</th>
<th>12 months</th>
<th>24 meses</th>
<th>36 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change of $\text{HbA}_1c$ (%)</td>
<td>$-0.71$</td>
<td>$-0.90$</td>
<td>$-0.90$</td>
</tr>
<tr>
<td>Change of the basal insulin requirements (U/kg/day)</td>
<td>$-0.13$</td>
<td>$-0.10$</td>
<td>$-0.11$</td>
</tr>
<tr>
<td>Weight gain (kg)</td>
<td>1.7</td>
<td>2.8</td>
<td>3.1</td>
</tr>
</tbody>
</table>

$\text{HbA}_1c$: glycosylated hemoglobin; CSII: continuous subcutaneous insulin infusion.
istration of a corrector bolus in ketosis situation; therefore they require the short duration admission in the hospitalization ward of endocrinology, with good evolution. A patient showed two or more events of serious hypoglycemia. There have been technical complications in 27.8% of the patients, caused by a catheter failure in most of the cases.

Discussion
The treatment with CSII in our patients improves the glycemic control and keeps the improvement achieved during the treatment. The mean reduction of the HbA₁c compared to the basal is of −0.71% after 12 months of treatment. The meta-analysis performed by Jeitler et al. included 12 studies that compared the effect of the CSII with the MDI in adults with T1D. Six of these studies used the HbA₁c as a measurement method, in which a mean difference in the HbA₁c of −0.4% was obtained. (CI of 95%: −0.65 to −0.20) in favour of the patients treated with CSII. Retnakaran et al. compared the efficacy of the CSII and the MDI, proving the efficacy of the analogues of fast insulin in both treatments, and observed that the CSII was associated to an adequate metabolic control compared to MDI; the therapeutic effect was estimated comparing the percentage of the reduction in the HbA₁c obtained with CSII and MDI, that was of 0.35% (CI of 95%: −0.10 to 0.80; p= 0.08).

In the patients of our series, the requirements of the basal insulin decreased since the starting of the treatment and were kept stable throughout the follow-up, in a similar manner than the one observed in several studies performed in patients treated with CSII. In a study carried out by Hoogma et al., a relevant reduction was observed of the total dose on insulin at the end of the study. 0.53 IU/kg/day in the group treated with CSII versus 0.71 IU/kg/day in the group treated with MDI. Hanaire-Broutinger et al. obtained similar results, with a total final dose of insulin of 38.5 IU/kg/day with CSII versus 47.3 IU/kg/day with MDI. However, due to the lack of insulin used in the bolus, we cannot assess the change of the total dose of insulin in our series.

We observe a weight gain of 2.7 ± 4.8 kg after 3 years of treatment with CSII. The increase was of 1.6 kg (CI of 95%: 0.45-2.75; p= 0.008) after 6 months and no relevant correlation was obtained with the change of HbA₁c (coefficient of Pearson: p= 0.14). Ziegler et al. observed a relevant weight gain, with a higher BMI at the end of the study in the group treated with CSII (24.2 versus 22.5 with MDI). In another study that compared both therapeutic modalities, a not relevant gain determined by means of the final weight could be observed (98.1 kg with CSII versus 97.6 kg with MDI).

A finding that we consider important in our study was the obtaining of a better response to the treatment with CSII in the individuals with a worse glycemic control at the beginning of the treatment and a higher diabetes evolution time. This finding has also been described in other studies and this subgroup of patients has been included (those with the worst glycemic control in conventional therapy) has been considered a candidate group to receive treatment with CSII. The benefit of the passage to CSII increases when the basal HbA₁c is higher.

A model derived from the meta-analysis performed by Retnakaran et al. predicts that in a patient with basal HbA₁c of 10%, the CSII would reduce the HbA₁c in an additional 0.65% compared to the MDI in a patient with a basal HbA₁c of 6.5%. No relation was found between the reason of the indication and the later evolution.

Five of our patients showed ketoacidosis due in part to a catheter failure and not to the administration of a corrector bolus in ketosis situation. In fact, Hoogma et al. observed a lower number of adverse events in a group of patients treated with MDI compared to a group treated with CSII. Ziegler et al. observed that the onset of ketoacidosis per each 100 patients-year was higher in the group of CSII, but this difference was not relevant. The results available for the performance of the meta-analysis of Jeitler et al. indicated that there have not been differences in the adverse events between the groups treated with CSII and MDI.

The hypoglycemia is the greatest barrier to improve and achieve a strict glycemic control. In our series, a 2.7% of the patients had more than two events of hypoglycemia, and none of them was serious (loss of consciousness, need of help by a third person, administration of glucagon, convulsions, admission at emergency wards, etc.). Recently, Pickup and Sutton have demonstrated in a meta-analysis of randomized trials that the serious hypoglycemia index was lower during the CSII compared to the MDI, with a index ratio of 2.89 (CI of 95%: 1.45-5.76;
The reduction was higher in patients with initial index of serious hypoglycemas with MDI and in patients with a longer duration of diabetes. There have not been differences according to the used fast-acting insulin analogue.

There have been technical complications in 27.8% of the patients, caused mostly by a catheter failure without any relation to the different characteristics of the mentioned device. Some recent publications determine that certain events occur with a seldom frequency, as the pump dysfunction, the catheter infection, the irritation or the local uneasiness, though in other studies different results were found.

Since our study is observational, it is not possible to determine a cause-effect relation in the found associations. We have not either measured the parameters of the life quality.

Conclusions
In our experience with this modality of intensive therapy, a sustained improvement of the glycemic control in the evolution could be observed as well as the need of basal insulins as from the beginning of the treatment with CSII and during the follow-up.

The greatest decrease of HbA1c was associated to a longer time of evolution of the diabetes and a worse initial glycemic control.

A weight gain after the beginning of the treatment with CSII was observed.

Declaration of potential conflict of interests
C.M. Causso, M.J. Goñi, M. García, M. Toni, P. Munárriz and F.J. Basterra-Gortari state that there are no conflicts of interest as regards to the content of this article.

References