Continuous subcutaneous insulin infusion (CSII) using an external insulin pump for the treatment of type 2 diabetes

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Abstract
Continuous subcutaneous insulin infusion (CSII) using an external pump is widely used for the treatment of type 1 diabetes, but has been less evaluated in type 2 diabetes. This review analyzes the open-label as well as randomized controlled studies performed in type 2 diabetic patients. The efficacy of CSII is compared with multiple daily injections (MDI) in terms of glycaemic control, weight variation, insulin requirements, treatment satisfaction and hypoglycaemic events. CSII may be offered as an alternative treatment to type 2 diabetic patients with poor glycaemic control despite high-dose insulin requirements administered through MDI.

Keywords: External insulin pump; CSII; Type 2 diabetes; Intensified insulin therapy; HbA1c; Diabetes; Review

Résumé
Traitement du diabète de type 2 par perfusion sous-cutanée continue d’insuline par pompe externe.
L’administration sous-cutanée continue d’insuline par pompe externe est largement utilisée pour le traitement du diabète de type 1, mais son usage dans le diabète de type 2 est moins bien évalué. Cette revue analyse les études ouvertes et controlées réalisées dans cette indication, études qui à ce jour sont peu nombreuses. L’efficacité de la pompe à insuline est comparée aux multi-injections sous-cutanées, en termes d’équilibre glycémique, de variation pondérale, de besoins en insuline, de satisfaction du traitement et d’incidence des hypoglycémies. La pompe à insuline pourrait être une alternative intéressante chez les patients diabétiques de type 2 dont l’équilibre glycémique reste médiocre en dépit de l’administration de fortes doses d’insuline en injections sous-cutanées discontinues.

Mots clés : Pompe externe; Diabète de type 2; Insulinothérapie intensifiée; HbA1c; Diabète; Revue

1. Introduction
Type 2 diabetes is the result of progressive β-cell dysfunction in a chronic state of insulin insensitivity [1]. Such β-cell disturbance is characterized by kinetic abnormalities, including abolition of first-phase, and reduction and delay of late-phase insulin secretion, and reduction of the rapid secretory spikes characteristic of a normal insulin secretory pattern. Qualitative disturbances of insulin secretion are characterized by alteration of the ratio of insulin/proinsulin secretion by β cells at the cost of inactive proinsulin [2,3]. These abnormalities worsen with time in the natural history of β-cell dysfunction in type 2 diabetes, and explain the need for exogenous insulin administration in patients who fail to respond to oral hypoglycaemic agents (OHA) [4].

The use of external pumps in patients with type 2 diabetes is a recent practice compared with type 1 diabetic patients, and only a few studies have been published so far. In France, continuous subcutaneous insulin infusion (CSII) using an external pump is an alternative insulin therapy for type 2 diabetes. It has been validated by the French Health Authority, which provides pump reimbursement for the treatment, and a recent position statement has summarized French recommendations for the use of insulin pumps in type 2 diabetes [5]. This review discusses the use of insulin pump therapy, and its impact on glucose control and other
variables such as weight, insulin requirements, quality of life, hypoglycaemia and other adverse events.

2. Effect of continuous subcutaneous insulin infusion on glycaemic control

CSII is an alternative to multiple daily injections (MDI) in the strategy of insulin therapy intensification in type 2 diabetes, but guidelines for choosing between these treatments are still lacking. In contrast to the widespread use of CSII in type 1 diabetes, few studies are available for type 2 diabetes and the results are conflicting.

2.1. Open-label studies of continuous subcutaneous insulin infusion in type 2 diabetes

CSII was proposed by several authors in the 1980s as an effective tool for the treatment of type 2 diabetes with extreme insulin resistance and poor glycaemic control. In these studies, insulin was administered as a transient intravenous insulin infusion, which lowered mean glucose levels and insulin requirements by 40%. Such beneficial effects were attributed to the reduction of glucotoxicity, which has favourable effects on insulin secretion by β cells and insulin resistance in target tissues [6–8]. The use of intravenous insulin infusion for 4 weeks, followed by CSII for 1 year, was assessed by Pouwels et al. [9] in eight obese type 2 diabetic patients who were poorly controlled despite high insulin requirements (about 2 U/kg/day). This sequential treatment allowed near-normal glucose levels to be achieved within 12 ± 6 days, with a reduction of HbA1c from 12 to 8.9% and a 35% reduction in insulin requirements. The insulin sensitivity index, measured by the hyperinsulinaemic–euglycaemic clamp technique, was substantially improved (M value ∼2). After one year of CSII, the mean HbA1c was maintained at less than 8.5%. A pilot study by Wainstein et al. [10] of 10 patients with poor glycaemic control also demonstrated, after 40 weeks of CSII, an HbA1c decrease of 2%, despite a 20% reduction in insulin requirements. Use of the concentrated insulin preparation U-500 (500 IU/mL) may be offered to type 2 diabetic patients with inadequate glycaemic control despite very high insulin requirements [11,12]. In one study [12], this led to a significant reduction in HbA1c (−1.23%), with a 70% increase in the time spent in normoglycaemia as assessed by continuous glucose monitoring (CGM).

Recent ‘before/after’ interventional studies have emphasized the potential benefits of CSII on glycaemic control (Table 1). Edelman et al. [13] carried out a 16-week study in 58 patients with uncontrolled glucose levels (mean HbA1c 8.4 ± 1.3%) despite treatment with OHA in combination, basal insulin plus OHA or MDI, and observed a substantial -1.2% drop in HbA1c. Kesavadev et al. [14] carried out a 24-week study in 46 patients who had been using a basal/bolus regimen and observed a −0.5% decrease in HbA1c with CSII. Reznik et al. [15], in a longitudinal retrospective study of 102 poorly controlled diabetic patients treated by CSII (−1.5%), reported a significant decrease in HbA1c, whatever the previous insulin regimen, which was maintained during the 5-year follow-up period. However, a
baseline HbA1c < 8% was not associated with improvement of glycaemic control with CSII.

These open-label studies provide interesting information on the potential efficacy of CSII in the treatment of hyperglycaemia in type 2 diabetic patients, despite the limited conclusions due to their retrospective design [15] and the lack of a control group [13–15].

2.2. Controlled studies of continuous subcutaneous insulin infusion compared with multiple daily injections in type 2 diabetes

Only four randomized controlled studies have compared the relative effectiveness of CSII and MDI for lowering glucose (Table 2) [16–19]. Two of these studies were parallel-group studies that included type 2 diabetic patients (n = 132 and n = 107, respectively) with a mean age range of 55–66 years. Patients were moderately obese with a baseline HbA1c between 8 and 8.4%, and all had been previously treated with at least one daily insulin injection with or without OHA. Study duration was 6 and 12 months, respectively [16,17]. Treatment intensification lowered HbA1c by −0.46 and −0.62% (MDI and CSII, respectively) in the Raskin et al. study [16] while, in Herman et al. [17], the glucose-lowering effect was greater (−1.6 and −1.7% with MDI and CSII, respectively). Insulin requirements at baseline were about 0.7 U/kg/day in Raskin et al. (no data reported in Herman et al.), and remained at about 0.7–0.8 U/kg/day by the end of both studies. These studies demonstrated the similar efficacy of CSII and MDI regimens.

In contrast, two randomized crossover studies have shown the advantage of CSII compared with MDI. In these studies, obese type 2 diabetic patients (n = 17 and n = 29, respectively) were successively treated by CSII and MDI for periods of 12 and 18 weeks, respectively [18,19]. Treatment intensification was proposed after patients failed to respond to at least two insulin injections per day (NPH or premixed NPH plus rapid insulin analogues), and the mean baseline HbA1c was greater than 9% despite a mean insulin requirement of 1 U/kg/day. In these two studies, CSII was more efficient than MDI for lowering HbA1c (−1.2 vs −0.45%, respectively, in Berthe et al. [18] and −0.8 vs +0.4%, respectively, in Wainstein et al. [19]). In both studies, CSII also significantly reduced the glucose area under the curve, as measured by CGM, compared with MDI [18,19].

The discrepancy observed between the crossover and parallel-group studies could be explained by the greater severity of diabetes in the crossover studies, as evidenced by the higher baseline insulin requirements, the higher baseline HbA1c levels and the higher number of insulin injections in comparison to the parallel-group studies.

However, in terms of identifying those patients who are likely to respond well to CSII, the conclusions that can be drawn from these studies are limited due to the small size of the populations in the crossover studies and the lack of selective criteria in the parallel-group studies. Prospective trials comparing CSII and MDI in larger cohorts of patients with severe insulin resistance and poor glycaemic control are required to allow any definitive conclusions to be drawn as to the actual benefits of CSII over MDI in the treatment of hyperglycaemia in type 2 diabetes.

3. Effects of continuous subcutaneous insulin infusion on weight and body mass index

Most of the studies evaluating CSII in type 2 diabetic patients were short-term studies, lasting less than 6 months [13,14,16,18,19] or 1 year [9,17]. In the studies with a duration of less than 6 months, either no weight changes [14,18,19] or a slight weight gain (+1.7 to 1.9 kg) were observed [13,16] whereas, in the two studies lasting 1 year, a slight weight gain of around 2 kg was observed in one study [17] and no change in the other [8], although the small population size limited any conclusions in the latter study. In the four randomized studies comparing CSII and MDI, no significant differences in weight changes were observed between the two treatments [16–19]. However, one retrospective longitudinal study showed a mean weight gain of 4–6 kg over a 6-year follow-up period, but with a wide range of weight variation on an individual basis [15].

Intensification of insulin therapy is, therefore, accompanied by moderate weight gain, but pump therapy appears to provide no additional risks in comparison to MDI.

4. Effect of continuous subcutaneous insulin infusion on total insulin requirements

Of the eight studies that reported total insulin requirements at the end of treatment, seven found no significant changes in insulin doses compared with the period preceding CSII initiation [13–19], whereas only one reported lowering of the insulin dosage with CSII vs MDI treatment [9].

5. Treatment satisfaction and quality of life with continuous subcutaneous insulin infusion

Three studies reported on treatment satisfaction. In the two randomized parallel-group studies [16,17], scores for treatment satisfaction, diabetes impact and diabetes satisfaction improved over time in both CSII and MDI groups. The scores did not differ between groups in the older population [17] whereas, in the younger population, the CSII group showed greater improvement in overall treatment satisfaction compared with MDI [16]. Also, the SF-36 physical and mental composite score did not change significantly either within or between the older population groups [17]. In the study by Berthe et al. [18], the patients’ satisfaction subscores were comparable between CSII and MDI treatment at the end of each treatment period.

6. Hypoglycaemia and other adverse events with continuous subcutaneous insulin infusion

Hypoglycaemia is the major outcome for evaluating intensified insulin therapy in type 1 diabetes, and most studies have found a very low incidence of severe hypoglycaemia in patients using CSII [20,21]. A recent meta-analysis showed an advantage of CSII vs MDI, with an odds ratio for severe hypoglycaemia of 0.48 [21]. Although data on the incidence of
Table 2
Randomized controlled studies comparing continuous subcutaneous insulin infusion (CSII) and multiple daily injections (MDI) in type 2 diabetic patients.

<table>
<thead>
<tr>
<th>Authors, year [ref]</th>
<th>Design</th>
<th>No and patients’ characteristics (BMI, DD)</th>
<th>Antidiabetic treatment before CSII</th>
<th>Insulin requirement before CSII (U/kg/day)</th>
<th>HbA1c (%) before CSII</th>
<th>HbA1c (%) after CSII</th>
<th>Weight difference (kg)</th>
<th>Type of insulin, average insulin requirement</th>
<th>CGM data</th>
<th>Non-severe hypoglyc (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raskin et al., 2003 [16]</td>
<td>Randomized parallel CSII vs MDI 24 weeks</td>
<td>n = 127, BMI: 32 DD: 12–14 years</td>
<td>Insulin + OHA: 41% insulin only: 59%</td>
<td>0.69 ± 0.75</td>
<td>8.2 ± 8 %</td>
<td>7.6 ± 7.5 % (NS)</td>
<td>+1.7 ± 0.8 (NS)</td>
<td>MDI/asp + NPH</td>
<td>NA</td>
<td>54 vs 59 % (NS)</td>
</tr>
<tr>
<td>Herman et al., 2005 [17]</td>
<td>Randomized parallel CSII vs MDI 48 weeks</td>
<td>n = 98, BMI: 32 DD: 15–17 years</td>
<td>Insulin + OHA: 43% insulin only: 57%</td>
<td>NA</td>
<td>8.4 ± 8.1 %</td>
<td>6.6 ± 6.4 % (NS)</td>
<td>+2.1 ± 2.6 (NS)</td>
<td>MDI/lispro+glargine</td>
<td>NA</td>
<td>81 vs 90 % (NS)</td>
</tr>
<tr>
<td>Wainstein et al., 2005 [19]</td>
<td>Randomized crossover CSII vs MDI 2 x 12 weeks</td>
<td>n = 29, BMI: 30–45 DD: 2–3 daily injections</td>
<td>&gt; 1</td>
<td>10.2% &amp; 10.3% (groups 1 and 2)a</td>
<td>-0.4% ± 0.8%*</td>
<td>-0.04 ± 0.09</td>
<td>CSII/lispro MDI/regular + NPH metformin both groups -15 U/day ± 20 U/day</td>
<td>Hyperglyc AUC</td>
<td>6 vs 20 % (NS)</td>
<td></td>
</tr>
<tr>
<td>Berthe et al., 2007 [18]</td>
<td>Randomized crossover CSII vs MDI 2 x 12 weeks</td>
<td>n = 17, BMI: 33.7 DD: 16.8 years</td>
<td>2 daily injections</td>
<td>1</td>
<td>9%</td>
<td>-1.3 ± 0.4%***</td>
<td>No change (both groups)</td>
<td>CSII/lispro MDI/lispro + NPHx3 1 U/kg/day, stable in both groups</td>
<td>Hyperglyc AUC</td>
<td>41 vs 47%</td>
</tr>
</tbody>
</table>

BMI: body mass index (kg/m²); DD: diabetes duration; CSII: continuous subcutaneous insulin infusion; MDI: multiple daily injections; CGM: continuous glucose monitoring; OHA: oral hypoglycaemic agents; NPH: neutral protamine Hagedorn; NA: not available; asp: aspart; hyperglyc/hypoglyc: hyperglycaemia/hypoglycaemia; AUC: area under the curve. *P < 0.01; **P < 0.03.

a Patients randomized to begin with either CSII or MDI (groups 1 and 2, respectively).
hypoglycaemia in type 2 diabetes are scarce, the two parallel-group studies— which lasted for 6 and 12 months, respectively [16,17]—showed a very low incidence of severe hypoglycaemia, if any (no event in Raskin et al. and 2.3% in Herman et al. [16,17]). In the latter study, the event rate per patient-year was 0.1 vs 0.2 for CSII vs MDI, respectively, with a trend towards significance in favour of CSII. In addition, the incidence of mild hypoglycaemia was similar in both groups (1.1 vs 1.2 per patient-week with CSII vs MDI, respectively) [17]. In Raskin et al. [16], a non-significant reduction was observed with CSII compared with MDI (0.8 vs 1.2 per patient-month, respectively). The nocturnal hypoglycaemia rate was similar in both treatment groups [16]. The percentages of patients reporting at least one minor hypoglycaemic episode in these two studies were also similar for both treatments (Table 2) and, in the two crossover studies [18,19], the same percentage of patients reported at least one hypoglycaemic episode (Table 2). The 24-h CGM recordings in the Berthe et al. study [18] showed no differences in hypoglycaemic duration between the two treatment groups. Other adverse events reported with CSII were hyperglycaemia [16], injection-site reactions [16,17] and technical problems [17].

7. Use of continuous subcutaneous insulin infusion in newly diagnosed type 2 diabetes

In newly diagnosed type 2 diabetic patients, prolonged hyperglycaemia per se may have deleterious effects on β-cell secretory capacity and target-tissue insulin sensitivity [22,23]. Ilkova et al. [24] were the first to propose that limiting the time spent by these patients in severe hyperglycaemia via short-term intensive insulin treatment with CSII might improve β-cell function and induce prolonged diabetes remission. Remission of diabetes in this setting is accompanied by recovery and preservation of β-cell function, as assessed by C-peptide stimulated secretion levels [25]. These observations were recently confirmed in a randomized controlled study involving 382 newly diagnosed type 2 diabetic Chinese subjects, where the interventional groups received short-term (2-week) courses of intensified insulin therapy by either MDI or CSII compared with conventional OHA therapy. The two intensified groups (MDI and CSII) were quicker to achieve normoglycaemia (4 and 9 days, respectively), and had higher remission rates than the OHA group (51 and 45 vs 27%, respectively) at the 1-year follow-up. Also, β-cell function, as assessed by HOMA-B, was significantly improved after the intensive insulin course, and the acute insulin response remained improved at the 1-year follow-up compared with the OHA group [26]. These findings highlight the benefit of rapid normoglycaemia by preserving β-cell function in type 2 diabetes.

8. Use of continuous subcutaneous insulin infusion during pregnancy

Insulin pump therapy may be offered to pregnant women with gestational diabetes mellitus or type 2 diabetes who either fail to obtain adequate glycaemic control with a basal/bolus regimen, have very high insulin requirements or experience persistent accelerated fetal growth despite an optimal conventional MDI regimen. When 30 women from a large study population were treated by insulin pump during pregnancy, the result was a rapid improvement of glycaemic control in almost 80% of them, with no hypoglycaemic episodes, but at the cost of greater weight gain and insulin requirements [27].

9. Use of continuous subcutaneous insulin infusion in insulin allergy

Despite the widespread use of human recombinant insulin and/or highly purified insulin preparations, insulin allergic reactions may still occur in type 1 and type 2 diabetes patients. Indeed, there have been case reports of localized or generalized allergic manifestations in type 2 diabetes successfully treated by CSII and a lispro analogue [28,29]. Nevertheless, data for the mechanism(s) behind antigenicity/immunogenicity modulation with continuous administration of subcutaneous insulin are scarce [29].

10. Use of oral hypoglycaemic agents with continuous subcutaneous insulin infusion

The use of OHA may be beneficial in type 2 diabetes patients who require intensive insulin therapy to promote better glycaemic control, reduce insulin requirements and limit weight gain [30]. However, few studies have tested such an hypothesis in CSII-treated type 2 diabetic patients. Metformin and sulphonylurea may be helpful adjuncts to CSII for long-term maintenance of HbA1c-lowering and may help to limit some procedures for pump management [31]. Limiting the use of CSII to only the night-time period may be proposed for patients who fail to achieve fasting glycaemic control with OHA [32]. Nevertheless, there are no randomized controlled studies reported in the literature testing the advantages of oral therapy as adjuncts to CSII in the management of type 2 diabetes.

11. Use of continuous subcutaneous insulin infusion in clinical practice: possible indications

Health-economic evaluations of CSII have been conducted for the treatment of type 1 diabetes and have shown that CSII, in comparison to MDI, increases the mean direct lifetime costs by approximatively 30%. However, interestingly, it was also demonstrated that the excess treatment costs with CSII were partially offset by reduced costs for complications [33]. As such a demonstration is not available for the use of CSII in type 2 diabetes, future studies need to address this question. Guidelines from the European and American diabetes associations are available, and propose progressive intensification of insulin therapy in type 2 diabetics who fail to respond to multiple OHA therapy. However, while a basal/bolus regimen using rapid and slow insulin analogues is described as the cornerstone of intensified insulin therapy [34], no mention is made of pump therapy as an alternative. Yet, pump therapy represents a more physiological way to administer insulin, and may be beneficial in type
2 diabetic patients who fail to respond to an intensified MDI course.

The profile of patients most likely to benefit from CSII includes severe chronic hyperglycaemia despite high daily insulin requirements as, when seen together, they indicate severe insulin resistance and β-cell exhaustion. Such patients are usually obese and have more abdominal fat, and do not respond to nutritional counselling for restricting carbohydrate and/or fat intakes; reducing post-meal excursions with CSII should limit hyperglycaemic peaks and their deleterious consequences on diabetes complications [35]. Pump therapy may also be offered to patients who need at least two injections a day with MDI [5], and may be an alternative to the thrice-daily premixed NPH/rapid analogue combination or the basal/bolus regimen of a slow-release analogue combined with a rapid-acting analogue in a regimen of 4–5 injections/day. When such patients fail to respond to CSII using an external pump device, an implanted pump therapy may help to reduce glycaemic variability and low-rate hypoglycaemia, and improve body weight, compared with MDI [36]. Other indications of CSII use in type 2 diabetics might be insulin resistance/very high insulin requirements, insulin allergy and pregnancy [5].

12. Conclusion

Pump therapy is a potentially useful approach for intensification of insulin therapy in type 2 diabetics. Despite the scanty and somewhat discrepant results of studies available so far, CSII may still be preferable to MDI in type 2 diabetic patients with severe insulin resistance and poor glycaemic control. In such patients, pump therapy is associated with a limited incidence of adverse events and weight gain, although predicting any given patient’s response is not possible. Prospective randomized studies are necessary to further analyze the impact of CSII on the pathophysiological mechanism(s) implicated in the hyperglycaemia of type 2 diabetes, and to define more precisely which subgroups of patients are more likely to benefit from switching from MDI to CSII.

Conflict of interest statement

Yves Reznik has carried out clinical trials as co-investigator for Medtronic, Eli Lilly and Novo Nordisk, and has provided advisory services to Medtronic, and attended conferences organized by Eli Lilly and Medtronic as a contributor.

References


