Original Article

A NOVEL USE OF U-500 INSULIN FOR CONTINUOUS SUBCUTANEOUS INSULIN INFUSION IN PATIENTS WITH INSULIN RESISTANCE: A CASE SERIES

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ABSTRACT

Objective: To report our experience with use of U-500 regular insulin (U-500) for continuous subcutaneous insulin infusion (CSII) in four patients with type 2 diabetes requiring high-dose insulin.

Methods: We performed a retrospective review of medical records of four patients with type 2 diabetes and insulin resistance who were using U-500 in a CSII regimen for at least 6 months. Before treatment conversion, two patients were receiving CSII with use of insulin lispro, and two were receiving multiple daily insulin injections. Clinical assessment was monitored with glycosylated hemoglobin (HbA1c) levels. Changes in the insulin volume administered and associated cost savings are analyzed.

Results: Three months after conversion to U-500 therapy, the average HbA1c decreased from 10.8% to 7.6%. By 6 months, it declined further to 7.3%. With use of U-500, the absolute volume of insulin infused per day decreased by at least fourfold. This volume reduction led to potential cost savings for insulin of up to $2,600 per year per patient and a savings for pump supplies of up to $3,400 per year per patient. All patients had subjective improvement in quality of life.

Conclusion: We propose that smaller volumes of insulin with use of U-500 allow for more efficient absorption of large doses of insulin and yield improved glycemic control. In our four patients, the use of U-500 for CSII resulted in improved quality of life, cost savings for treatment, and potential reduction in diabetes-related complications based on the decline in HbA1c. This treatment method may be a novel alternative for patients with type 2 diabetes and insulin resistance who have not met goal glycemic control with standard intensive regimens or who require insulin doses exceeding current insulin pump delivery capacity. **(Endocr Pract. 2003;9:181-186)**

Abbreviations:
BMI = body mass index; **CSII** = continuous subcutaneous insulin infusion; **HbA1c** = glycosylated hemoglobin; **MDII** = multiple daily insulin injections; **U-500** = regular insulin with 500 U/mL

INTRODUCTION

With the results of the Diabetes Control and Complications Trial (1) and the United Kingdom Prospective Diabetes Study (2), we know that intensive glycemic control of diabetes mellitus can significantly delay the onset and progression of many complications associated with type 1 and type 2 diabetes mellitus. The two methods most commonly used to achieve "tight" glycemic control in patients with type 1 diabetes are continuous subcutaneous insulin infusion (CSII) and multiple daily insulin injections (MDII). Various orally administered agents and subcutaneous insulin regimens are typically used for type 2 diabetes. Some patients with type 2 diabetes, however, fail to attain reasonable control with available orally administered medications and standard insulin regimens. Reasons for this lack of glycemic control may include obesity, comorbid conditions, concurrent medications, inadequate dietary restraint, sedentary lifestyle, and insulin resistance. For patients with insulin resistance, these factors may contribute to significant escalations in the insulin dose, and such patients may require more than 200 U of insulin per day.

Although the use of CSII has traditionally been reserved for patients with type 1 diabetes, CSII is currently being used with increasing frequency in type 2 diabetes. CSII may be prescribed for patients with wide fluctuations in glucose levels, frequent episodes of hypoglycemia limiting intensive therapy, inability to meet target glycemic goals with use of standard therapies, and lifestyles that require increased flexibility (3,4). The recent revisions put forth by the American College of Endocrinology recommending a target glycosylated hemoglobin (HbA1c) level

Submitted for publication July 24, 2002
Accepted for publication October 1, 2002
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The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Navy, the Department of Defense, or the United States Government.
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of <6.5% will likely result in further increases in insulin requirements for many of these patients to achieve these new goals (5)

The standard insulin preparations used for CSII by means of an insulin pump contain 100 U of insulin per milliliter (U-100). Velosulin BR human insulin (Novo Nordisk) has been used in the past for CSII but has essentially been replaced by insulin lispro (Lilly) or insulin aspart (Novo Nordisk). U-500 regular insulin (Humulin, Lilly) is a formulation containing 500 U of regular insulin concentrated into each milliliter. U-500 regular insulin (U-500) is occasionally used subcutaneously for patients with high insulin requirements. We found only one case report in the literature that mentioned use of U-500 insulin for CSII, and that was in a patient with extreme insulin resistance requiring 10,000 U of insulin per day (6). Use of a surfactant-stabilized U-400 human insulin preparation has been reported for intraperitoneal delivery and implantable pump systems only (7,8). We report a retrospective review of four patients with type 2 diabetes and insulin resistance whose treatment regimen had been converted to U-500 administered by means of CSII.

PATIENTS AND METHODS

Study Cohort

We retrospectively reviewed the data of four patients with type 2 diabetes whose treatment was changed to U-500 insulin administered by means of CSII after target glycemic control levels were not achieved by other reasonable means. Two patients had been receiving MDII, and two patients were already using CSII with a U-100 insulin lispro preparation. All patients had at least 6 months of follow-up after initiation of this regimen. All subjects participated in an extensive insulin pump training program. Basal rates were adjusted for a goal fasting plasma glucose level of 70 to 110 mg/dL and were changed if glucose levels fluctuated more than 30 points on 3 repetitive assessments. Boluses were individualized on the basis of a sliding scale and carbohydrate count regimen. Goal 2-hour postprandial plasma glucose levels were 140 mg/dL or less. Patients chose either the Disetronic (Minneapolis, MN) or the Minimed (Sylmar, CA) pump on the basis of personal preference.

Illustrative Cases

Patient A

A 40-year-old man was diagnosed as having type 2 diabetes in 1992. His body mass index (BMI) was 32 kg/m^2. He was also being treated for hypertension, dyslipidemia, and hypothyroidism. An initial course of sulfonylureas had been ineffective, and he was subsequently treated with escalating doses of insulin. For the next several years, his glycosylated hemoglobin level remained above 21% despite use of 225 U of insulin in a split NPH and regular insulin regimen. Mild retinopathy, neuropathy, and nephropathy complicated his course. A change in treatment to a split regimen consisting of Ultralente insulin and insulin lispro yielded minimal improvement. Despite the addition of troglitazone and metformin at maximal doses, his HbA1c remained between 12.0 and 15.9%. A left plantar foot ulcer then developed that persisted for the next 18 months despite aggressive wound care and podiatry evaluation. Multiple magnetic resonance images and bone scans showed no evidence of osteomyelitis. His employment involved variable shift work that made compliance with a regimen of MDII difficult. Furthermore, the patient could not keep syringes in his workspace. Therefore, he was offered CSII to facilitate better compliance. Because his blood glucose levels consistently approximated 500 mg/dL, he was admitted to the hospital and received inpatient pump training and monitoring. Before conversion of his treatment to CSII, he was using 64 U of Ultralente insulin twice daily and 45 U of insulin lispro three times a day before meals for a total of 263 U per day. With use of U-100 insulin, his necessary dose for boluses would generally exceed the hourly delivery capacity of his insulin pump. Moreover, he would be required to change his cartridge daily if using nearly 300 U per day, and he was unable to do this at his workplace. Therefore, U-500 insulin was used in the insulin pump. His rosiglitazone dosage of 8 mg daily was continued, as was the simvastatin therapy (80 mg daily). Three months after conversion to CSII with use of U-500, his HbA1c had decreased from 14.0% to 9.0%. By 4 months and 8 months, it declined further to 7.4% and 7.0%, respectively. His quality of life subjectively improved primarily because of removal of insulin injections and resolution of hyperglycemic symptoms, and his foot ulcer finally began to heal.

Patient B

A 56-year-old man with type 2 diabetes, diagnosed in 1989, initially underwent assessment in the endocrinology clinic in May 2000. At that time, he was taking metformin (2,500 mg daily) and 70/30 insulin (85 U twice daily), and his HbA1c level was 7.5%. His BMI was 34 kg/m^2. He already had diabetic retinopathy, neuropathy, and coronary artery disease. His other medical conditions included psoriasis, hypertension, dyslipidemia, and rheumatoid arthritis. The latter two diagnoses were treated with simvastatin (60 mg) and fenofibrate (200 mg daily) and twice weekly injections of etanercept, respectively. His glycemic control was complicated by wide fluctuations in his glucose levels, with three to four hypoglycemic episodes per week. In March 2001, his HbA1c was 9.1%, and CSII therapy with U-100 insulin lispro was begun. After extensive education and evaluation, his total insulin requirement, including basal rates and boluses, was calculated as 250 U per day. The metformin was discontinued. The patient was a nurse anesthetist, and hyperglycemia was developing during unexpected long cases because his cartridge would run out of insulin. One month after initiation of insulin pump therapy with use of insulin lispro, his treatment was changed to U-500 to decrease the frequency of cartridge changes and prevent further hyperglycemia. Approximately 3 months after conversion to

U-500 therapy, his HbA1c decreased to 7.0%, and by 6 months, it was at 5.7%. His overall quality of life substantially improved because of resolution of his hypoglycemic and hyperglycemic episodes and less frequent insulin cartridge changes.

Patient C

A 37-year-old woman with a history of hypertension and asthma was diagnosed with type 2 diabetes in 1997. Her BMI was 30 kg/m^2. She was initially treated with insulin, and then a trial of oral hypoglycemic therapy which was ineffective. During the next 2 years, her asthma necessitated frequent use of prednisone, which aggravated her already poor glycemic control. On initial assessment at our clinic, she had polyuria and polydipsia. Her HbA1c was 11.2% despite use of 130 U of NPH insulin and 8 mg of rosiglitazone daily. Metformin was added at maximal dose. Her insulin was titrated upward, and she ultimately was requiring 630 U of insulin per day, consisting of 200 U of NPH insulin twice daily, 85 U of regular insulin before breakfast and dinner, and 60 U of regular insulin before lunch. She was requiring at least seven insulin injections daily and was developing painful accumulation of insulin at the injection sites. Her blood glucose levels still exceeded 200 mg/dL. Because of this increasingly high insulin requirement and the patient's motivation to control her diabetes, she was considered a good candidate for an insulin pump. After she received extensive education and training from our diabetes educator, CSII was initiated. She would have required at least a total daily dose of 630 U of insulin with use of the standard U-100 formulation. This insulin requirement exceeded the delivery capacity of the insulin pump for premeal boluses and would necessitate cartridge changes at least twice daily. For these reasons, U-500 insulin was used with the initiation of CSII. One month after she began the U-500 regimen, her HbA1c decreased to 8.0%, and by 3 months, it had declined to 6.1%. It subsequently increased to 7.7% but then declined to 6.6% at 10 months. During the first day of CSII therapy, she experienced nausea and vomiting when her plasma glucose level reached 120 mg/dL. Her basal rates were adjusted accordingly. She had one episode of hypoglycemia during the first 10 weeks that prompted a visit to the emergency department, but no major complications occurred. Her hyperglycemic symptoms resolved, and her overall quality of life subjectively improved.

Patient D

A 54-year-old man who had had type 2 diabetes for 18 years was first examined in our clinic in 1991 and started on insulin therapy in 1994. His BMI was 34 kg/m^2. During the next 3 years, he was diagnosed as having diabetic retinopathy and neuropathy, which resulted in a severe bilateral foot pain syndrome. Troglitazone was added to his insulin regimen, which consisted of 130 U of 70/30 insulin per day. Metformin was used briefly without improvement and subsequently discontinued, as was the troglitazone when his therapy was changed to MDII. For the next several years, he was treated with increasing doses of Ultralente insulin and insulin lispro. In February 2000, his HbA1c was 11.8%, and he was considered for a CSII regimen. At that time, he was receiving 40 U of Ultralente insulin twice daily and 20 U of insulin lispro before meals three times daily. He continued using the insulin pump with lispro for 1 year, and his HbA1c reached a nadir at 8.1%. Nevertheless, he was requiring 192 U of insulin per day and was having leakage at the insertion site. Because of the problem with insulin leakage and a lack of significant progression to goal HbA1c, his CSII was changed to U-500 insulin. He continued to take atorvastatin, 30 mg daily, for dyslipidemia. His HbA1c before treatment conversion was 9.0%. After 3 months of U-500 therapy, his HbA1c decreased to 8.3%, but at 6 months, it had increased to 8.9%. This result was probably due to lack of compliance with basal rate adjustments. Interestingly, his hypoglycemic awareness returned, and he noted a considerable decrease in the neuropathic foot pain. His quality of life improved because of fewer cartridge and insertion site changes.

Cost Analysis

Cost savings analysis for insulin was based on wholesale prices and not federal government prices. We used the following price quotes for our calculations: $47.70 for a 10-mL vial of insulin lispro (Lilly) and $181.99 for a 20-mL vial of U-500 regular insulin (Lilly). Cost savings analysis for pump supplies was based on the actual patient cost provided from the manufacturers, with an estimated cost of $11.00 per infusion-insertion set and $3.00 for each reservoir or cartridge. We used an average cost of $14.00 for each change in setup.

RESULTS

All four of our patients had type 2 diabetes in conjunction with insulin resistance and had been using U-500 regular insulin for CSII for at least 6 months before our retrospective review. In our review, we were searching for clinical benefits but also wanted to investigate the cost-effectiveness of this U-500 regimen. Patients A and C were receiving MDII before conversion to CSII; for the reasons described, the insulin pump therapy was initiated with use of U-500. Patient B had used U-100 (lispro) for CSII for 1 month before treatment was changed to U-500, and patient D had used U-100 (lispro) for CSII for 1 year before treatment was converted to U-500. The insulin requirements and associated volume to administer that dose of insulin before and after conversion to U-500 therapy are summarized in Table 1. The total insulin dose with U-500 therapy was recorded at the 6-month time frame.

The total daily insulin requirements for patients A and C decreased from 263 U and 630 U to 153 U and 249 U, respectively. The total daily insulin requirements for patients B and D basically remained unchanged (the dose increased from 250 U to 253 U in patient B and from 192

Table 1
Insulin Requirements in Study Patients

	Before U-500*		After U-500*	
Patient	Insulin (U/day)	Volume (mL/day)	U-500 (U/day)	Volume (mL/day)
A	263†	2.63	153	0.307
B	250‡	2.5	253	0.507
C	630§	6.3	249	0.497
D	192‡	1.9	199	0.397

*U-500 = regular insulin with 500 U/mL.
†Ultralente insulin and insulin lispro.
‡Insulin lispro in continuous subcutaneous insulin infusion.
§Ultralente insulin and regular insulin.

U to 199 U in patient D). The absolute volume infused per day decreased by at least fourfold in all our patients. This decrease in volume is depicted in Figure 1. Because U-500 regular insulin is 5 times as concentrated as U-100 regular insulin, the volume to administer a specific dose with use of U-500 should be one-fifth the volume with use of U-100. Inasmuch as the daily insulin requirements for patients B and D remained essentially unchanged, the volume administered with use of U-500 was approximately 20% of the volume required with use of insulin lispro, as expected.

We were interested in determining whether changing to U-500 therapy was cost-effective for both the insulin and the pump supplies. In light of the fact that each cartridge or reservoir holds approximately 3 mL of insulin regardless of the type of insulin used, most of our patients would need to change their cartridge daily. Patient C would have been required to change her setup twice a day to administer the calculated 6 mL of insulin per day. By diminishing the volume required to administer daily insulin, the frequency of cartridge changes decreased from at least once per day to every 3 days, even though the supply of insulin may have lasted longer. All patients were instructed to change their cartridge and insertion set every 3 days on the basis of manufacturer recommendations even if the cartridge was not empty or to change the insertion set anytime they changed their cartridge. This approach not only subjectively improved the quality of life for our patients but also provided substantial cost savings potential. Reducing the pump supplies by 50 to 66% could yield potential cost savings in pump supplies alone of up to $3,400 per year per patient. This estimate is based on an average change in pump supplies costing $14.00.

U-100 costs $4.77 per milliliter of insulin. U-500 costs $9.10 per milliliter of insulin. In contrast, however, U-100 costs $4.77 per 100 U of insulin, whereas U-500 costs $1.82 per 100 U of insulin. Despite U-500 costing more per milliliter, the dramatic reduction in volume of insulin used in all patients yielded potential cost savings of up $2,600 per year per patient. The cost savings for insulin in patients A and C were likely underestimated because we directly compared the cost of U-100 versus U-500 using the much lower insulin dose with use of U-500. These calculations do not account for any cost savings from the reduction of risk associated with overall improved glycemic control. For comparison, insulin aspart costs $5.41 per 100 U and Velosulin costs $3.90 per 100 U.

Clinical improvement was assessed by HbA1c measurements and subjective changes reported by the patients. The HbA1c levels before and after changing to U-500 therapy are shown in Figure 2. HbA1c was assessed at least 3 and 6 months after initiation of U-500 therapy. The average HbA1c declined from 10.8% to 7.6% after 3 months (mean reduction of 3.2%). Six to 8 months after conversion to U-500 therapy, the HbA1c declined further to 7.3% (mean reduction of 3.5%). Patient D had the smallest change in HbA1c but still reported symptomatic improvement. Of note, patient D was noncompliant with basal rate adjustments.

All four patients reported improvements in their quality of life with use of the insulin pump. This outcome was primarily due to improved glycemic control and removal of multiple insulin injections each day. Nevertheless, even the two patients already receiving CSII with use of U-100 reported further improvement after changing to U-500. Again, this result was not only due to diminished clinical symptoms with better glycemic control but also due to resolution of insulin leakage at the subcutaneous insertion site and fewer set changes. Hypoglycemia is a known complication of intensive therapy. Only one hypoglycemic episode that necessitated emergency evaluation was reported. This occurred in patient C and resolved quickly; hospital admission was not necessary. Interestingly, despite having only minimal change in his HbA1c, patient

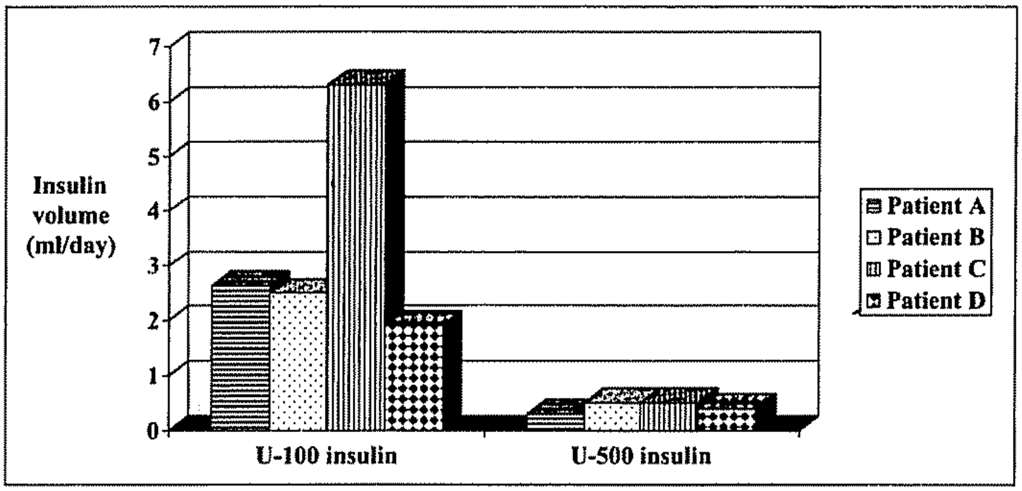

Fig. 1. Change in volume of insulin infused per day with adjustment from U-100 to U-500 insulin therapy in four patients.

D experienced a return of his hypoglycemic awareness and an appreciable decrease in his painful peripheral neuropathy after using U-500. No similar improvement was noted during use of the insulin pump for the preceding year with U-100 lispro.

The only potential adverse outcome noted was an increase in BMI in three of the four patients. The BMI was recalculated approximately 6 months after initiation of use of the U-500 regimen. The BMI (kg/m^2) increased from 32 to 36 in patient A, 30 to 35 in patient C, and 34 to 35 in patient D. The BMI in patient B remained at 34. Unfortunately, waist:hip ratios were not determined. All patients except patient C were receiving a statin for dyslipidemia. Patient B was receiving both a statin and fenofibrate. The individual lipid-lowering regimens did not require change, and retrospective review of available lipid profiles did not demonstrate obvious trends. Nevertheless, because we reviewed only four patients and each patient was receiving a different regimen, no meaningful analysis is possible.

DISCUSSION

Our retrospective review led to two important findings. First, HbA1c decreased in all patients after administration of U-500 by CSII for a minimum of 6 months. The average HbA1c decreased from 10.8% to 7.3%. The mean reduction in the HbA1c value was 3.5%. Few if any medical regimens have yielded such a reduction in HbA1c levels. Furthermore, two patients reached the target HbA1c

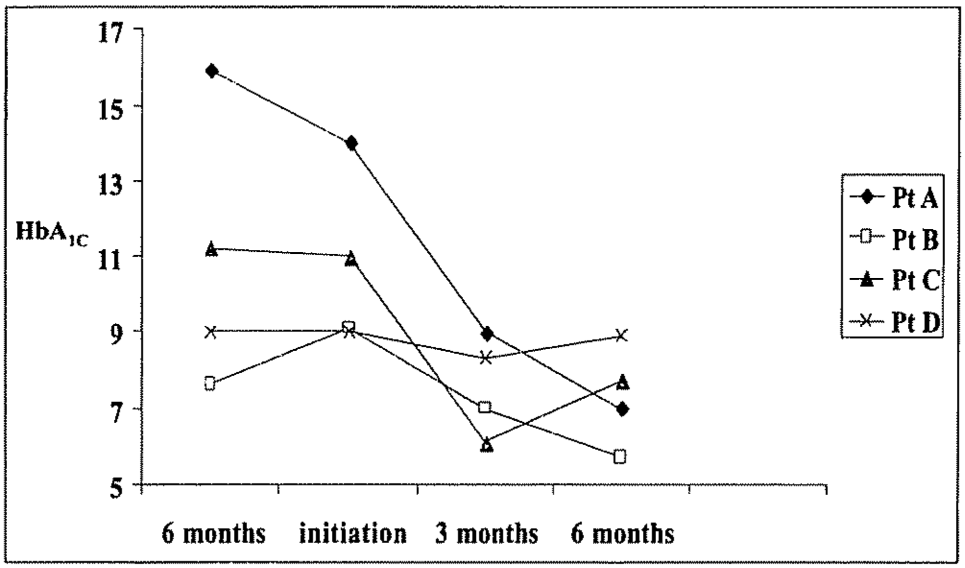

Fig. 2. Glycosylated hemoglobin (*HbA1c*) levels (measured as percentages) relative to initiation of U-500 insulin therapy in a continuous subcutaneous insulin infusion regimen in four patients

goal of <6.5% during treatment. Data from the United Kingdom Prospective Diabetes Study demonstrated a 37% reduction in risk for microvascular complications and a 21% decrease in the risk of any end point or death related to diabetes for every 1% decrease in HbA1c (2,9). On the basis of the decrease in HbA1c experienced by most of our patients, they have strong potential for a reduction in future diabetes-related complications. The scenario with patient D emphasizes the fact that health-care providers must carefully select motivated and appropriate candidates for CSII.

Second, the smaller volumes needed with use of U-500 insulin resulted in fewer changes in the pump cartridge and insertion sets. This situation led to subjective improvement in our patients' quality of life as well as potential cost savings for both insulin and pump supplies. These cost savings were estimated to be $6,000 or more per year per patient. U-500 requires less volume than U-100 to deliver the same dose of regular insulin. The use of U-500 allowed delivery of the sheer magnitude of insulin required by our patients. We hypothesize that the smaller volumes also allowed for more efficient, predictable absorption and delivery of insulin by means of CSII in our patients with such high insulin requirements.

Our two patients who had already been receiving CSII maintained nearly the same daily dose of insulin using either U-500 or lispro but experienced a change in volume to administer that dose. Our two patients previously receiving MDII had benefit in both a greater than expected decrease in their total daily insulin requirements and the associated decrease in volume to deliver that dose. Initiation of insulin pump therapy itself is unlikely to have accounted for all the improvements noted because the two patients already using an insulin pump but previously receiving U-100 lispro derived additional benefit after the conversion to U-500 therapy.

Of course, we cannot exclude any benefit of using the U-500 regular insulin preparation in and of itself. Jorgensen et al (10) compared absorption of human NPH insulin given subcutaneously to pigs as a U-100 versus a U-500 formulation. They noted that the absorption of a specific insulin dose was substantially delayed by changing the insulin concentration from U-100 to U-500. This provided a fivefold increase in concentration of the same NPH preparation.

CONCLUSION

We have presented a case series of four patients with type 2 diabetes and insulin resistance who demonstrated improved glycemic control and decreased symptoms with the use of U-500 insulin for CSII. Obviously, our experience is limited to only four patients, and this treatment strategy will need further evaluation. In light of our optimistic findings, however, we propose that U-500 regular insulin for CSII is a viable and novel alternative for patients with type 2 diabetes and insulin resistance who are not meeting glycemic goals with use of their current CSII regimen or who would have difficulty using one of the available U-100 insulin preparations because of high insulin requirements. In the future, it would be interesting to compare directly the use of U-100 regular versus U-500 regular insulin for CSII and to evaluate the need for other insulin concentrations such as "U-250" as well. Although not available from our data, clinicians may consider measuring C-peptide levels before and after therapy with U-500 insulin to assess any improvement in beta-cell function and the underlying insulin resistant state.

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