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Evaluation of a Conservative Pharmacist-led U-500R Insulin Management Protocol in the Primary Care Setting

Cyndi Dumont[1], Leah Fitzgerald[1], and Connie A. Valdez[1]

Abstract

Objective: The objective of this quality assurance study is to evaluate the impact of a conservative, pharmacist-led, U-500R insulin management protocol on diabetes control (A1c) and total daily dosage requirements between August 2016 and August 2018. **Methods:** This was a retrospective chart review of adult patients, aged 18 to 79, with type 2 diabetes and managed with insulin, at 2 federally qualified healthcare clinics in Denver, Colorado. To determine if our conservative pharmacist-led U-500R insulin management protocol impacted efficacy and total daily dosage requirements when converting patients from U-100 to U-500R insulin, we compared the most effective dose of U-500R (defined as the total daily dose (TDD) of U-500R insulin at A1c goal or the lowest tolerated A1c) to the baseline A1c and TDD of U-100 insulin at time of conversion. **Results:** Following conversion of U-100 to U-500R insulin, patients required an average of 21 fewer units of insulin with U-500R than U-100 and achieved an average A1c of 7.2% which reflected a reduction of 3.5 points from baseline. Five patients (62.5%) achieved A1c goal per ADA guidelines, and all patients achieved at least a 1.7 point reduction in A1c, with 1 patient achieving a 6.7 point reduction. Two patients (25%) were still in the process of U-500R titration at the time of data collection, and 1 patient (12.5%) did not achieve goal A1c while under pharmacy management at these clinics. Four of the five patients who achieved A1c goal did so with an overall reduction in total daily insulin dose (average of 57.5 units less than original U-100 dose) resulting in an average A1c decrease of 3.6 points.

Keywords

concentrated insulin, U500, diabetes mellitus, Type 2, drug therapy, insulin resistance, primary care, collaborative drug therapy management, pharmacist

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Introduction

Achieving optimal blood glucose (BG) control in patients with Type 2 diabetes mellitus and severe insulin resistance can be challenging. These patients often require large volumes of U-100 insulin which may lead to altered absorption and leakage during administration.[1] An alternative approach to large insulin doses is to transition from U-100 insulin to human (regular) 500 units/mL insulin (U-500R).[2] This option is often desirable since smaller volumes are required of U-500R, as the insulin is 5 times more concentrated than U-100 insulin. Because smaller volumes are injected with the U-500R product, insulin leakage can be minimized, thus improving insulin absorption, patient comfort, and A1c. Most patients will have improved glycemic control using twice daily U-500R, but the precise dosing regimen depends on the total daily insulin requirements of the patient.[3,4] However, because U-500R is highly concentrated, many providers in primary care settings will not prescribe U-500R, but prefer to refer patients to be managed by endocrinology. When patients are unable to receive specialty care from endocrinology due to financial constraints or when endocrinology practice sites are closed to new

[1]University of Colorado Anschutz Medical Campus, Aurora, CO, USA

Corresponding Author:
Connie A. Valdez, Skaggs School of Pharmacy and Pharmaceutical Sciences, Sheridan Health Services, University of Colorado Anschutz Medical Campus, 12850 E Montview Blvd., Aurora, CO 80045, USA.
Email: Connie.valdez@cuanschutz.edu

patients, management of diabetes remains in the primary care setting. This situation occurred at 2 federally qualified healthcare centers where patients who had severely insulin resistant, uncontrolled diabetes were managed by their primary care provider, because they were unable to access endocrinology specialty care. Fortunately, these 2 clinics provided interprofessional patient care, which included a clinical pharmacist who split her time between the 2 practice sites. In 2013, a decision was made to develop a pharmacist-led program to help primary care providers address this gap. A U-500R insulin protocol for clinic use was created to guide insulin conversion, titration and management, since manufacturer dosage guidance was not available at that time other than the package insert that stated U-500R is to be dosed 2 to 3 times daily. In 2013, the manufacturer provided no guidance for converting patients from U-100 insulins to U-500R.

The clinical pharmacist collaborated with the clinic's primary care providers and diabetes educators to develop a Collaborative Drug Therapy Management (CDTM) pharmacist-led U-500R insulin management program. This program included a conservative dosing conversion process as part of the U-500R insulin management protocol which prioritized safety, because U-500R is the most concentrated insulin available on the US market. The U-500R insulin management program was implemented in 2013 at both clinics and has been reserved for patients who have severe insulin resistance and are unable to schedule an appointment with endocrinology (either due to endocrinology clinics not accepting additional Medicaid patients or based on financial constraints for patients who are uninsured). Criteria for initiation into the U-500R insulin management program includes patients who have minimal or no mental cognitive impairment, are receiving 200 units or more of insulin daily, can recognize and appropriately manage hypoglycemic episodes and are adherent with clinic visits. Per protocol, upon initiation of a patient into the U-500R insulin program, a pharmacist calculates the patient's total daily U-100 insulin dose and reduces that dose by 20% to determine the starting dose of U-500R. Patients are instructed to inject 60% of the total daily U-500R dose 30 minutes before breakfast and the remaining 40% 30 minutes before dinner. Patients are required to demonstrate appropriate insulin administration technique prior to initiating U-500R, and the pharmacist uses the teach-back method to ensure patient understanding. Patients are then followed by pharmacy services for insulin titration based on blood glucose values and tolerability.

More recently, in 2015, the manufacturer of U-500R has provided a dosing conversion algorithm, based on a study by Hood et al., the U-500 Initiation Trial.[2,3] The algorithm recommends initiating U-500R at 100% of the patient's U-100 total daily dose (TDD) if their A1c is greater than 8% and the mean self-monitored plasma glucose $\geq$183 mg/dL during the week preceding the initiation of U-500R. Despite the current availability of a dosing conversion algorithm provided by the manufacturer, our clinics have continued to use the conservative pharmacist-led U-500R dosing protocol which empirically reduces the total daily insulin dose by 20% regardless of A1c values. This decision was made to ensure patient safety, as there is a paucity of data supporting the 1:1 dosing conversion for patients with an A1c greater than 8% as recommended by the manufacturer. Thus, the objective of this quality assurance study is to evaluate the impact of a conservative pharmacist-led U-500R insulin management protocol on diabetes control (A1c) and total daily dosage requirements.

Methods

This was a retrospective chart review of adult patients managed by clinical pharmacy services at 2 underserved primary care clinics in Denver, Colorado. This initiative was approved as exempt by the Colorado Multiple Institutional Review Board. Patients were included if they were aged 18-79 and were using U-500R to manage type 2 diabetes between August 2016 and August 2018. Patients were excluded if they were initiated on U-500R prior to receiving care at one of these 2 clinics, if the patients' U-500R insulin regimen was not managed by pharmacy services or if U-500R was newly initiated and had not yet been titrated. Patient charts were reviewed by a designated clinical pharmacist at both study sites. Data collection included patient demographic information (ie, age, sex, weight, BMI), A1c goal based on the ADA guidelines, TDD of U-100 insulin at time of conversion, initial dose of U-500R, and most effective dose of U-500R (defined as the TDD of U-500R insulin at the time of achieving A1c goal or the lowest A1c).

To determine if our conservative pharmacist-led U-500R insulin management protocol impacted efficacy and total daily dosage requirements when converting patients from U-100 to U-500R insulin, we compared the most effective dose of U-500R to the baseline A1c and TDD of U-100 insulin at time of conversion. Descriptive analysis was completed for all variables evaluated except for data regarding A1c control which was analyzed using Fisher's exact test with an a priori significance level of 0.05.

Results

Thirteen patients met initial inclusion criteria. Four patients were excluded because their U-500R dosing was not managed by pharmacy services and another patient was excluded because U-500R had been initiated but not yet titrated at the time of chart review—leaving a total of 8 patients included in the case series. The average age of patients was 59 years (50% male), and the majority of patients had a goal A1c of less than 7%. At baseline, patients had an average A1c of

Table 1. Baseline Characteristics.

	Average N (%)
A1c	10.7
Age	59
Female	4 (50)
Average TDD of U-100 (units)	258
Goal A1c <7%	6 (75)
Goal A1c <8%	2 (25)
Weight (lbs)	265
BMI	37.8

10.7% and required an average of 258 units of U-100 insulin (Table 1), with no patients having an A1c below 8% at the time of conversion. The U-500R doses were titrated according to our clinic protocol until goal A1c was achieved or further titration could not be tolerated. According to clinic protocol, all patients were initiated at 80% of their total daily U-100 pre-conversion insulin dose. Five patients (62.5%) achieved maximum A1c reductions on a U-500R dose that was lower than their pre-conversion U-100 insulin TDD (Figure 1). Of those patients, the average reduction in TDD was 18% at the time of maximum titration with 4 of the 5 achieving goal A1c. In the 3 patients who required more units of U-500R compared to the pre-conversion U-100 dose, the average increase was 30 units, or a 12% increase from pre-conversion U-100 TDD (Figure 2). There was a non-significant reduction in A1c between patients who required a lower dose of U-500R versus, those who required a higher dose (−3.2 vs −3.9 $P < .8088$). Overall, patients required an average of 21 fewer units of U-500R than of U-100 and achieved an average A1c of 7.2% which reflected a reduction of 3.5 points from baseline (Table 2). Five patients (62.5%) achieved A1c goal per ADA guidelines, and all patients achieved at least a 1.7 point reduction in A1c, with 1 patient achieving a 6.7 point reduction. Two patients (25%) were still in the process of U-500R titration at the time of data collection, and 1 patient (12.5%) did not achieve goal A1c while under pharmacy management at these clinics. Four of the five patients who achieved A1c goal did so with an overall reduction in total daily insulin dose, an average of 57.5 units less than original U-100 dose resulting in an average A1c decrease of 3.6 points.

Discussion

The results of this study illustrate how a conservative, pharmacist-led, U-500R insulin management program was effective in improving A1c in the majority of patients and at lower total daily dosage requirements of U-500R compared to U-100 insulin. On average, A1c was reduced from 10.7% to 7.2% following the conversion of U-100 to U-500R. Most importantly, 62.5% of patients achieved maximum A1c reductions on a final U-500R dose that was lower than their pre-conversion U-100 insulin TDD. Specifically, 80% of the patients who achieved their A1c goal did so with a reduction in total daily insulin dose by an average of 57.5 units less than their original U-100 dose. Although not all patients reached their A1c goal, patients who had an overall improvement in A1c required a lower total daily dose of insulin by 21 units. All patients included in the study were highly insulin resistant with uncontrolled type 2 diabetes and were unable to access specialty care with endocrinology. Had the providers decided to initiate U-500R based on the current manufacturer's algorithm, all of the patients included in this study would have qualified for a 1:1 conversion from U-100 to U-500R, and it is possible that harm from hypoglycemic events may have occurred in these patients. Having a conservative, pharmacist-led, U-500R insulin management program allowed for patient access to a highly concentrated insulin as well as safe and effective management of each of these patients.

There is a paucity of literature demonstrating the role of clinical pharmacists in the management of U-500R insulin other than providing collaborative care (eg, patient education, clinical consults) which primarily occurs in the hospital setting. This study is unique, as it illustrates the outcomes of a pharmacist-led U-500R insulin management program on reductions in patient A1c and on U-500R insulin dosage requirements in the primary care setting, where pharmacists can independently manage U-500R under protocol. However, it is important to note that the role of the clinical pharmacist extends beyond the insulin conversion and management of patients transitioned to U-500R. Similar to the pharmacist-led U-100 rapid insulin titration program at each of these clinics, patients enrolled in the pharmacist-led U-500R insulin management program receive intensive lifestyle coaching on a weekly or bi-weekly basis. These coaching sessions likely enhance positive patient outcomes as related to diabetes control as well as safety. Because U-500R is a highly concentrated form of insulin, close follow-up upon conversion of U-500R is critical. With more frequent monitoring, patients also receive more intense lifestyle monitoring, education, coaching and reinforcement. Improved lifestyle choices may lead to weight loss, which in turn often leads to reduced insulin requirements. Reduced insulin requirements in patients who are making positive lifestyle changes is another reason that a conservative dosing conversion algorithm may be important.

In the development of the pharmacist-led U-500R insulin management program, emphasis was placed on ensuring the formation of a conservative protocol, as there is a lack of published research evaluating dosing algorithms used to convert patients from traditional U-100 insulin regimens to U-500R insulin. It was assumed that patients may need a lower amount of U-500R compared to U-100 insulin which is why we compared the U-100 and U-500R total daily

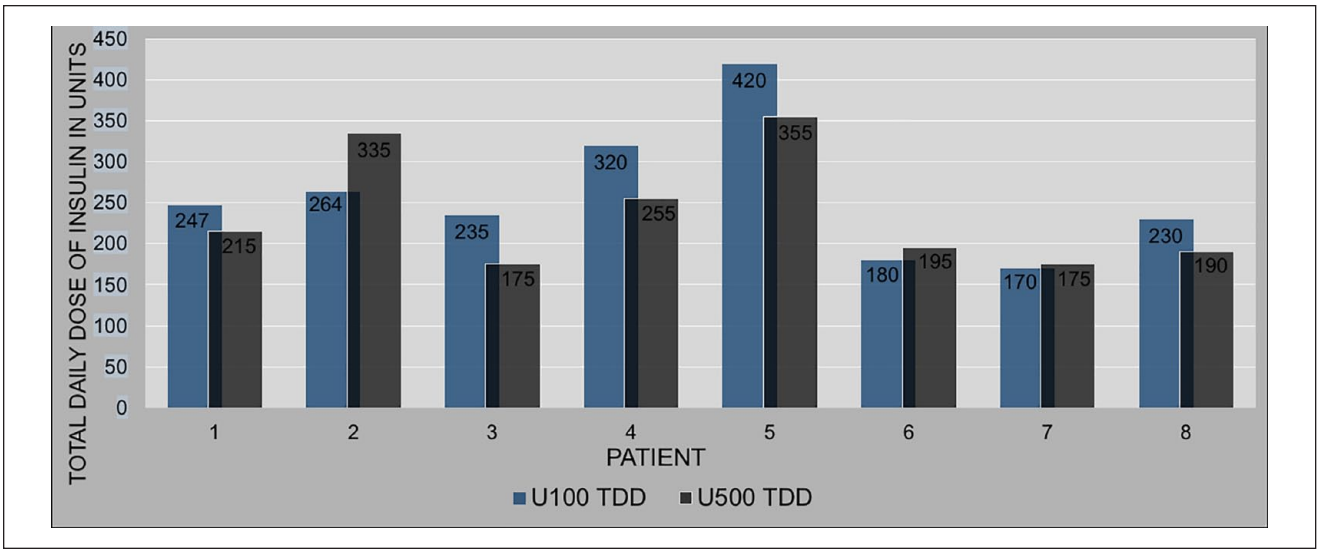

Figure 1. Comparison of total daily dose (TDD)of insulin in 8 patients, from time of U-100 insulin conversion to the most effective dose of U-500R insulin.

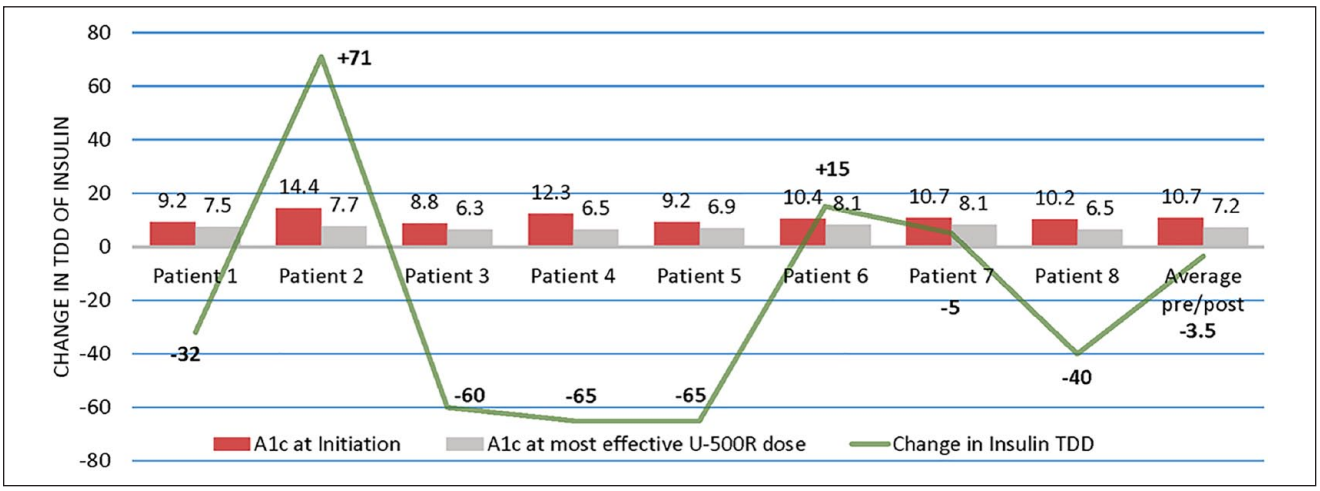

Figure 2. Relationship between reduction in A1c percentage (bars) and change in total daily dose (TDD, solid lines) of insulin in 8 patients who transitioned from U-100 insulin (blue bar) to U-500R insulin (gray bar).

Table 2. Comparison of patient characteristics pre and post U-500R initiation.

	Pre U-500R initiation average	Post U-500R initiation average	Change from pre to post U-500R initiation
A1c (%)	10.7	7.2	−3.5
Average TDD of insulin (units)	258	236	−22
Weight (lbs)	265	245	−20
BMI (lbs/in^2)	37.8	37.1	−0.7

dosage requirements. Lilly based its conversion algorithm on the Hood et al study, which evaluated the efficacy of twice daily dosing compared to thrice daily dosing of U-500R. In this study, a formula used to convert patients from U-100 to U-500R was altered when the A1c was below 8%—yet there was no rationale provided for this reduction. In addition, the decision to use a 1:1 TDD for patients with an A1c greater than 8% was not elucidated.[3] Without

literature to support the outcomes of these dosing algorithms, safety was determined to be uncertain. Other clinical reviews and studies proposed methods to transition patients to U-500R, but these suggestions were based on small case reports or case series.[5-7] Published studies evaluated efficacy and side effects of U-500R insulin, but to our knowledge, there are no published studies whose purpose was to evaluate conservative dosage conversion strategies. Our study demonstrates that even with a 20% reduction in TDD of insulin during the transition from U-100 to U-500R, some patients required a further dose reduction. Without the initial dose reduction, it is possible that our patients may have suffered consequences from excessive hypoglycemia. We hope the results from this case series will help guide other primary care clinicians who are considering the use of U-500R for patients who are unable to access specialty care until more literature is available to evaluate the use of U-500R insulin in the primary care setting.

Limitations

A limitation of this study is the sample size, with only 8 patients who qualified for analysis. Additionally, the data was retrospective and descriptive. Furthermore, hypoglycemic episodes were not analyzed, so safety concerns are speculative. Lastly, although coaching sessions are provided to patients managed by clinical pharmacy services, we did not assess if patients were managed by pharmacy prior to the transition to U-500R. As such, coaching sessions may have additionally contributed to the reduction in A1c and insulin requirements for some patients studied. We realize the results of this study may not be applicable for most primary care clinics but are optimistic that this data could provide some guidance for other clinics that manage underserved patients who may not have access to specialty care.

Conclusion

The conservative pharmacist-led U-500R dosing protocol was an effective tool to transition patients from U-100 to U-500R insulin in the primacy care setting, as 62.5% of the patients converted to U-500R per protocol had a final U-500R dose lower than their pre-conversion U-100 TDD while achieving an average A1c reduction of 3.5 points. Furthermore, 66% of patients who achieved their goal A1c did so using fewer units of U-500R than of U-100.

Declaration of Conflicting Interests

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ORCID iD

Connie A. Valdez https://orcid.org/0000-0002-4963-3533

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