

Evaluating the Effect of U-500 Insulin Therapy on Glycemic Control in Veterans With Type 2 Diabetes

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■ IN BRIEF This article describes a single-center, retrospective chart review to determine the glycemic effect of converting from U-100 to U-500 regular insulin in veterans with type 2 diabetes and the effect of this change, if any, on the frequency of provider contacts. Results showed that U-500 insulin improved glycemic control without significantly increasing the risk of hypoglycemia or total daily insulin dose, even when follow-up contacts with providers were not structured or frequent.

More than 25.8 million children and adults in the United States have diabetes, accounting for 8.3% of the population. Type 2 diabetes comprises >90% of all diagnosed cases of diabetes (1). Underlying insulin resistance is a major contributor to the development and progression of type 2 diabetes, resulting in the eventual need for insulin therapy for glycemic control. Between 2007 and 2009, 26% of adults diagnosed with diabetes were on some type of insulin therapy (1). High doses of insulin are often required to overcome severe insulin resistance.

Severe insulin resistance is often defined as a situation in which a patient requires >200 units/day of insulin (2). However, attempting to achieve glycemic targets with standard U-100 insulin introduces potential limitations because of large volume requirements. These larger volumes may necessitate multiple injections per dose, with pain resulting from large depot formation. Leakage at the site of injection and potential for poor or variable tissue absorption may also be problematic. Such limitations may adversely affect

glycemic control and may indirectly influence it by decreasing adherence.

One approach to addressing these limitations includes the use of human U-500 (500 units/mL) concentrated regular insulin (hereafter referred to as “U-500 insulin”). Insulin of higher concentration, specifically U-500 insulin, has been on the market since 1952 as beef-derived insulin, but human-derived U-500 insulin was not marketed until 1997. It was not commonly used until more recently, to address insulin demand in highly insulin-resistant patients.

The pharmacokinetics of U-500 insulin have not been studied extensively in humans. However, limited studies have shown some significant pharmacokinetic differences between U-100 and U-500 insulin. Compared to less concentrated regular insulin formulations, U-500 has a greater time to insulin peak concentration (1.75–8.5 hours) and a longer duration of action (6–24 hours) (3–8). Therefore, it may be dosed as little as twice a day because of its longer duration of action. Time to onset of action, however, is similar between U-500 and U-100 regular

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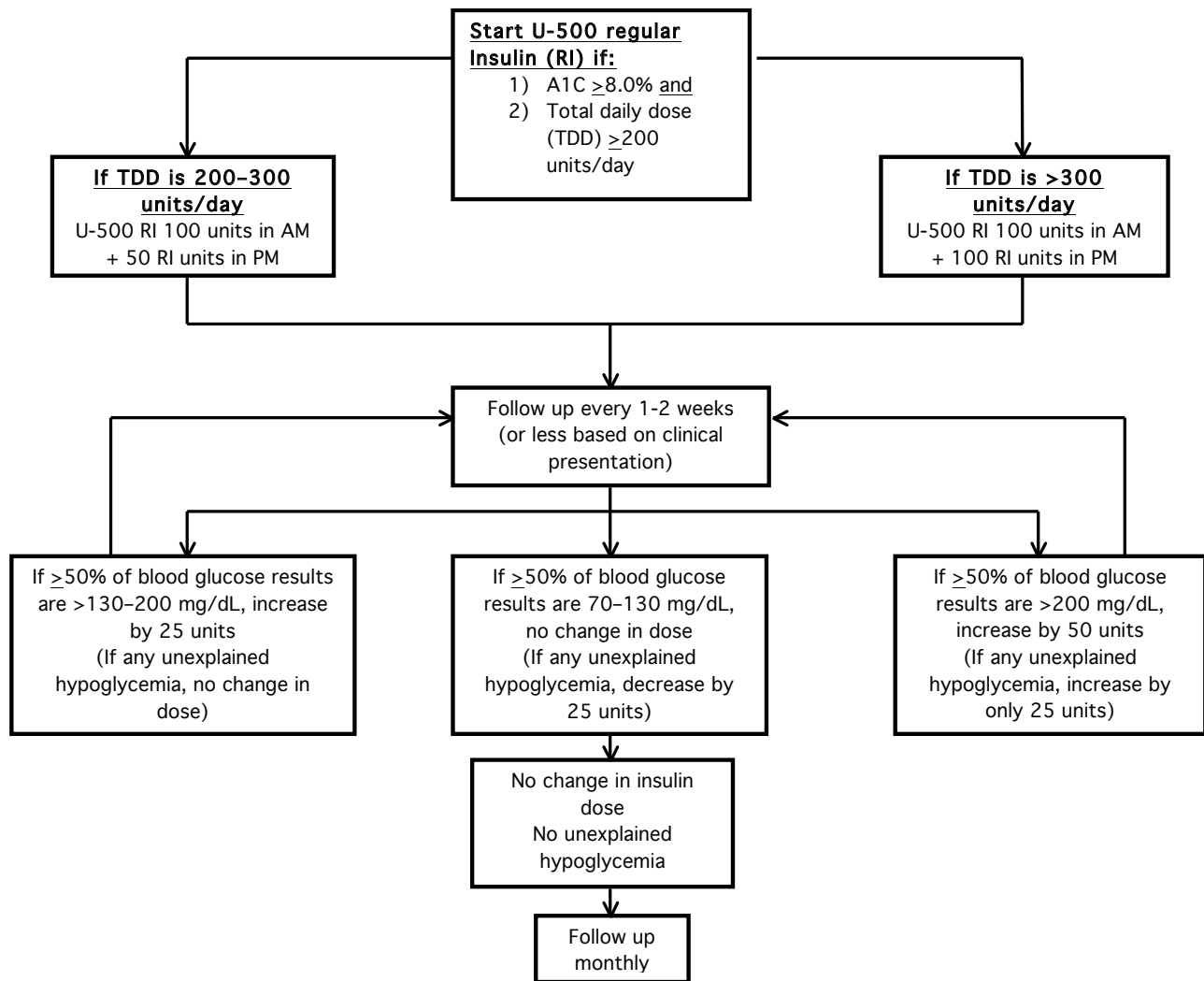
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■ **FIGURE 1.** Suggested protocol for conversion to U-500 insulin, adapted from Ref. 10 and author's experience. Initial twice-daily dosing is for patient convenience and to lessen the number of injections per day. Dose titration and more frequent injections (three to four per day) may be required for some patients based on fasting, preprandial, and postprandial blood glucose levels. U-500 regular insulin should be administered at least 30 minutes before a meal. Close monitoring and frequent follow-up are highly encouraged until glucose levels are stable and patients have no unexplained hypoglycemia.

insulin (~30 minutes) (8). In general, U-500 insulin displays both basal and prandial properties. Thus, the utility of U-500 insulin is significant in patients with severe insulin resistance; it provides a means of addressing the aforementioned limitations of U-100 insulin in these patients by decreasing the number of injections and volume of insulin per injection, and thus improving adherence to the insulin regimen.

Clinical efficacy data for U-500 were also scant until the 2000s.

Present data are limited to information gathered through retrospective or observational studies. Multiple retrospective studies have assessed U-500 insulin's effect on A1C, weight change, total daily dose of insulin, and number of daily injections. Three studies evaluating the efficacy of U-500 insulin in the veteran population have been published, all of which found a significant reduction in A1C in patients who were converted from U-100 to U-500 insulin (9–11). Two of these three studies used a specific

U-500 insulin protocol along with structured approaches to management and follow-up (Fig. 1) (10,11). However, none assessed whether the frequency of follow-up influenced the effect of converting from U-100 to U-500 insulin on glycemic control.

Increase in the use of U-500 insulin at our facility in the past 5 years prompted our interest in evaluating its efficacy and safety in our veteran population at the New Mexico VA Health Care System (NMVAHCS). Because our institution, unlike those

in some previous studies, lacks a protocol for U-500 monitoring and follow-up, our study would potentially provide us with a better idea of the clinical efficacy and safety of U-500 insulin use in a more practical health care setting.

The aim of our study was to retrospectively review the charts of patients who were switched from U-100 to U-500 insulin and to assess changes in A1C from the time of conversion to ≥ 2 months after conversion. Additionally, to determine whether provider follow-up played a role in changes in glycemic control, the secondary examined was change in the frequency of provider contacts. In cases where the frequency of provider contact changed, we examined whether the change correlated to a change in A1C. Additional parameters assessed included changes in weight, rate of hypoglycemic episodes (both objective and subjective), insulin dose, and number of daily injections.

Methods

This study was a single-center, retrospective chart review of patients prescribed U-500 insulin between 1 April 2009 and 1 February 2013 after evaluation by the NMVAHCS endocrine service. The inclusion dates for chart review were chosen secondary to a U-500 insulin process change that occurred in March 2009, which involved a mandatory appointment with a registered nurse/certified diabetes educator (RN/CDE) for patient education before starting U-500 insulin therapy. This appointment entailed a review of insulin concentration and dosing based on units and milliliters for tuberculin syringe use. U-500 insulin could only be initiated by members of the endocrine service, who are responsible for selecting eligible candidates based on their adherence to previous insulin therapy, their high insulin demand (total daily dose usually >200 units/day), and their intolerance to or current use of an insulin sensitizer. Additionally, U-500 in-

sulin required a nonformulary request and review by a clinical pharmacist, who would approve the request after another assessment for medication adherence on the U-100 insulin regimen, appropriateness of U-500 insulin therapy and dose, and assurance of appropriate insulin education.

A list of patients prescribed U-500 insulin after 1 April 2009 was generated using the Veterans Integrated Service Network Data Warehouse on a Microsoft SQL server (Microsoft; Redmond, Wash.). The NMVAHCS computerized patient record system was used for screening and collecting patient data.

Patients were eligible for the study if they were evaluated by the endocrine service and converted from U-100 to U-500 insulin during the aforementioned inclusion dates with a minimum of one documented A1C measured ≤ 6 months before conversion and any subsequent A1C ≥ 2 months after conversion. Additionally, patients must have received initial insulin education by the RN/CDE and must have been followed by the NMVAHCS endocrine service after conversion. The number of provider contacts was collected starting 3 months before the first A1C recorded before conversion (baseline) and through the date of the final A1C recorded after conversion. Patient-provider contacts included in-person or telephone follow-up between patients and primary care physicians, endocrinologists, primary care nurses, or RN/CDEs that involved the adjustment of medication therapy. The number of contacts was adjusted to reflect a rate of contacts per 30 days.

Patient characteristics collected included weight, comorbid conditions, ethnicity, age, duration of diabetes, and any changes in renal or hepatic function. Total daily dose of insulin and number of injections were recorded at the time of conversion and at the time of the final A1C measurement. Chart-documented objective (<70 mg/dL) and subjective

hypoglycemic episodes were recorded starting 3 months before conversion and until the final A1C measurement. Similar to frequency of contacts, hypoglycemic episodes were also adjusted to reflect a per-month rate.

It was expected that patients were adherent to U-100 insulin therapy because that is one of the eligibility criteria for U-500 insulin use. Nevertheless, U-100 insulin adherence was evaluated along with U-500 adherence based on patients' pharmacy record refill history. Patients who refilled insulin on time $\geq 80\%$ of the time during the study period were considered adherent. Concomitant diabetes medications were recorded at the time of conversion to U-500 insulin and the most recent A1C. Any patient who stopped U-500 insulin in favor of another insulin therapy for a reason other than hospital admission was considered to have converted back to U-100 insulin.

Study approval was obtained through the University of New Mexico institutional review board and the NMVAHCS Research and Development Committee.

Statistical Analysis

Parametric data were analyzed using a paired *t* test. A Wilcoxon signed rank test was used to account for outliers in changes in A1C and contact frequency. A Spearman's rank correlation was applied to determine the presence of correlations between two variables. Results were considered significant at $P \leq 0.05$. All statistical analyses were performed using the Statistical Analysis System (SAS Institute, Cary, N.C.).

Results

Thirty-eight patients were prescribed U-500 insulin between 1 April 2009 and 1 February 2013. Twenty-five of these patients met the A1C inclusion criteria; 13 patients did not meet inclusion criteria. One of the 25 was initiated on U-500 insulin by the endocrine service at NMVAHCS but was followed at another VA facility. This patient was included in the

A1C analysis but was not included for the secondary outcome because the follow-up frequency could not be assessed.

Baseline patient characteristics are shown in Table 1. The mean age was 57 ± 8 years (range 41–70 years). The only female patient in the study was the patient who was not followed by the NMVAHCS endocrine service. Therefore, the secondary outcome only includes data from male patients ($n = 24$). The average duration of diabetes was 16 ± 8 years (range 3–40 years). A majority of the patients (60%) were white.

Results of the study are summarized in Table 2. The mean A1C level decreased from 9.4 to 8.7% ($P = 0.0343$) during the median follow-up period of 13 months (range 2–43 months). The mean frequency of provider contacts decreased from 2.8 to 1.7 per month ($P = 0.018$). Statistical analysis using a Wilcoxon signed rank test did not change the statistical significance of the change in A1C ($P = 0.0366$) or contact frequency ($P = 0.0112$). There were no significant changes in the mean rate of hypoglycemic events or total daily dose of insulin before conversion compared with after conversion. The mean number of injections per day significantly decreased from 5.0 before conversion to 2.7 after conversion ($P < 0.0001$). A statistically significant change in weight was seen, with a mean increase of 12 lb ($P = 0.02$). No significant correlation was found between change in A1C

TABLE 1. Baseline Patient Demographics

Age (years)*†	57 ± 8
Duration of diabetes (years)*†	16 ± 8
Male [n (%)]	24 (96)
Ethnicity [n (%)]	
White	15 (60)
Black	1 (4)
Native American	1 (4)
Unanswered	8 (32)

*Expressed as mean \pm standard deviation.

†As documented in computerized patient record system.

and change in contact frequency or weight gain.

The adherence rate decreased from 96% before conversion to 79% after conversion ($P = 0.046$). Five patients converted back to U-100 insulin because of frequent hypoglycemia on U-500 insulin ($n = 2$) or patient preference ($n = 3$). Their data was included up until their final A1C on U-500. No changes in renal or hepatic function were noted in any patients.

In terms of concomitant diabetes medications, only one patient was on another type of injectable medication at the time of the most recent A1C. Six of fifteen patients on an oral agent at time of conversion remained on an oral agent at the time of the most recent A1C. No new oral agents were initiated in patients who were not on an oral agent at the time of conver-

sion. Patients' comorbidities did not influence any findings.

Discussion

In this retrospective study, a significant reduction in A1C was found in highly insulin-resistant veterans with type 2 diabetes who were converted from U-100 insulin to U-500 concentrated regular insulin and were not subject to a strict management protocol. Although statistically significant, one may question the clinical significance of an A1C reduction that is $<1\%$ given that a reduction of $\geq 1\%$ has been well documented to be associated with a reduction in both micro- and macrovascular complications (12). Furthermore, previously published U-500 studies have shown A1C reductions of $\geq 1.0\%$ (9–11). One explanation for this is the role of duration of follow-up. The two studies that had reductions of 1.5% (9) and 1.7% (10) had shorter follow-up periods compared to our study (3 and 12 months, respectively). Because our study did not have a maximum duration of follow-up, it is possible that some patients experienced a more significant reduction in A1C within the first year after conversion and then experienced a tapering off of that glycemic control benefit, possibly because of the progressive nature of diabetes, increasing insulin resistance, or lifestyle changes (i.e., diet and exercise). Further evidence for this theory is one study that had a mean follow-up of 20 months and found only a 1.0% reduction in A1C (11). Additionally,

TABLE 2. Results

	Before Conversion	After Conversion	Mean Change	P
A1C (%)*†	9.4 ± 1.9	8.7 ± 1.7	-0.7	0.0343
Contacts (n/month)	2.8	1.7	-1.1	0.0184
Documented hypoglycemia (n/month)	0.7	1.1	0.4	0.0764
Insulin total daily dose (units/day)*	321 ± 99.6	330 ± 189	9	0.8799
Injections (n/day)*	5.0 ± 0.66	2.7 ± 0.79	-2.3	<0.0001
Weight (lb)*	281 ± 61.4	293 ± 73	12	0.02

*Expressed as mean \pm standard deviation.

†All results $n = 24$ except A1C, which was $n = 25$.

the average duration of diabetes may dampen the glycemic effect of switching to U-500 insulin. The average duration of diabetes in our study (16 ± 8 years) was longer than in other published studies (i.e., Quinn et al., with a duration of 9.1 ± 5.7 years and Zeisler et al., with a duration of 14 ± 7 years) (10,11). These findings suggest that our patients had more severe insulin resistance.

Because of the potential risk of hypoglycemia associated with U-500 insulin use, possible dosing errors related to its concentrated formulation, and additional follow-up from the endocrine service, it was anticipated that we would find at least a marginal increase in the frequency of contacts after conversion compared to before conversion. The reason for the significant decrease in provider follow-up is likely multifactorial. One reason may be that many patients had multiple appointments with primary care providers or the endocrine service before converting to U-500 insulin in an attempt to optimize their U-100 insulin regimen. Second, one of the reasons for consideration for U-500 insulin is poor glycemic control, which may require more frequent follow-up from providers. Because a significant improvement in glycemic control was seen after conversion to U-500 insulin, one could postulate that with better control comes a decreased need for frequent follow-up. Third, another contributor to the finding of a decrease in follow-up frequency may have been underestimation of follow-up contacts after conversion. The number, duration, and causes of hospitalizations were not collected, although some patients were hospitalized during the study period. The number of contacts per month was not adjusted to account for time spent in an inpatient setting, thus potentially resulting in a reduction of the mean rate. To account for these confounders in a future study, similar time

frames should be used to determine the per-month rate of contacts.

A significant reduction in A1C without an increase in hypoglycemia or dose of insulin may indicate better utilization of injected insulin secondary to a more concentrated, lower-volume of injection solution. To further corroborate this, a significant increase in weight indicated better absorption of insulin. It is well established that insulin therapy can lead to weight gain.

As found in Quinn et al. (10), there was a significant reduction in the number of injections per day. Although not assessed in this study, reduced number of injections can potentially result in increased patient satisfaction and adherence.

The reason for the reduction in adherence rate is likely a case of regression to the mean. Because U-100 insulin medication adherence was evaluated by the endocrine service and a clinical pharmacist, it was expected that all patients were adherent to their previous diabetes regimen before converting to U-500 insulin. Additionally, because adherence was determined by pharmacy database refill history, some patients may have been using U-500 vials for longer than the manufacturer's 31-day recommendation. As a result, reduced adherence may have been the result of a knowledge deficit regarding appropriate insulin handling. It is uncertain what impact reduced adherence had on A1C change.

As with many retrospective studies, this study had some limitations. First, patients served as their own controls. In addition, the study had a relatively small sample size, which consisted mostly of older men. The sample size likely would have been larger if patients prescribed U-500 insulin before 1 April 2009 were included. However, before this date, patients were not required to receive RN/CDE education before starting U-500 insulin. We did not include these patients to maintain consistency in the education level of the

patients included in the study. Other limitations include the inability to fully and accurately assess patient adherence and to identify potential insulin self-adjustments. Patients who were admitted to the hospital at any point during the study period may or may not have received U-500 insulin. This could have resulted in A1C levels that did not reflect sole U-500 therapy. Finally, there was a wide range in insulin doses and in multiple clinician involvement, both of which may have influenced glycemic control.

Conclusion

This study provides further evidence that U-500 insulin offers a significant A1C reduction even when follow-up contact is not structured or frequent. In addition, the frequency of documented hypoglycemia was not significantly increased in patients who converted from U-100 to U-500 insulin. Better glycemic control, as represented by A1C, along with similar insulin doses and increased weight gain, provides further evidence that U-500 insulin may allow for better utilization of injected insulin than large volumes of U-100 insulin.

We recommend that patients with type 2 diabetes who require ≥ 200 units/day of U-100 insulin and are adherent to, but not well-controlled on, their current insulin regimen, be considered for U-500 insulin therapy. We endorse a multidisciplinary approach involving RNs, pharmacists, and CDEs to support endocrinologists, primary care providers, and patients, as well as to select ideal candidates. Patients should receive appropriate counseling on the basic differences between U-100 and U-500 insulin, know how to calculate and draw up doses to avoid medication errors, and demonstrate proper administration technique. As always, providers should assess patients' willingness and ability to change insulin regimens and encourage self-care behaviors such as self-monitoring of blood glucose, eating a healthful diet,

exercising, and adhering to medication regimens.

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Duality of Interest

No potential conflicts of interest relevant to this article were reported.

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