Duration of Insulin Supply in Type 1 Diabetes: Are 90 Days Better or Worse Than 30 Days?

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ABSTRACT

Objective. There have been few studies regarding the duration of insulin prescriptions and patient outcomes. This study evaluated whether A1C varied with the duration of insulin prescription in patients with type 1 diabetes.

Methods. We conducted a longitudinal investigation (from 2001 to 2015) within a nationwide private health insurer. A cohort study was first used to compare A1C after 30-day only, 90-day only, and a combination (30-day and 90-day) of insulin prescriptions. Second, a self-controlled case series was used to compare A1C levels after 30-day versus 90-day prescriptions for the same person.

Results. In the cohort study, there were 16,725 eligible patients. Mean A1C was 8.33% for patients with 30-day prescriptions compared to 7.69% for those with 90-day prescriptions and 8.05% for those who had a combination of 30- and 90-day prescriptions (P <0.001). Results were similar when stratified by age and sex. Mean A1C was 7.58% when all prescriptions were mailed versus 8.21% when they were not. In the self-controlled case series, there were 1,712 patients who switched between 30- and 90-day prescriptions. Mean A1C was 7.87% after 30-day prescriptions and 7.69% after 90-day prescriptions (P <0.001). Results were similar when stratified by sex. For this within-person comparison, the results remained significant for those ≥20 years of age (n = 1,536, P <0.001), but not for youth (n = 176, P = 0.972).

Conclusion. There was a statistically significant but clinically modest decrease in A1C with 90-day versus 30-day insulin prescriptions in adults. A mailed 90-day insulin prescription may be a reasonable choice for adults with type 1 diabetes.

For patients with stable type 1 diabetes, refilling an insulin prescription often involves receiving either a 30-day or 90-day supply. Currently, many insulin prescriptions are obtained through mail order as 90-day supplies. Overall, prescription expenditures from mail-order pharmacies exhibited a 6.7% increase from 2015 to 2016 in the United States (1). The actual duration of insulin supply for any given prescription is complex because dosing depends on patients' physical activity, daily variations in dietary intake, concurrent illness or injury, and use of other medications (2,3). A 30-day insulin supply may or may not last for 30 days.

Moreover, transitional times between refills may, on occasion, be problematic. When a patient is traveling or when circumstances are such that a pharmacy pick-up would be difficult, a refill can be requested early or transferred to a different pharmacy. Such procedures vary across pharmacies and insurance plans but, if there is an inadequate understanding of

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these policies, the time between refills may present a challenge for some patients. Beyond the potential problems associated with timely access, there may be concerns regarding shipment. Insulin is a biodegradable protein and requires proper storage to maintain integrity (4). Thus, there may be questions with a shipment of 90-day insulin that is left on the doorstep when the summer temperatures are high or winter temperatures are freezing. There also may be issues with timely delivery, especially if a patient is changing addresses. With these issues in mind, we designed a longitudinal investigation to examine whether 30-day versus 90-day prescriptions of insulin are associated with A1C levels. It was unclear, at the onset of the study, which of these approaches would be preferable because there are potential advantages and disadvantages to either method.

Methods

Data were obtained through the Clinformatics Data Mart Database (OptumInsight, Eden Prairie, Minn.), from 1 January 2001 through 30 June 2015. This nationwide database contained integrated longitudinal health information on 61.8 million individuals in the United States who had private health insurance and included demographic and membership information, outpatient visits, hospitalizations, pharmacy records, and laboratory data.

Eligibility criteria included at least two diagnosis codes specific to type 1 diabetes (*International Classification of Diseases*, 9th Revision, Clinical Modification codes 250x1 or 250x3) with no use of antidiabetic medications except for insulin. Because we wished to measure A1C in patients who had completed initial insulin titration and were more likely to use stable doses of insulin, we also made the stipulation that A1C values were recorded ≥1 year after type 1 diabetes

TABLE 1. A1C by Duration of Insulin Prescription: Between-Patient Comparison

		A1C			Predicted A1C, %	
Variables	***n***	**B**	**95% CI**	***P***	**Mean**	**95% CI**
Overall						
Duration of prescription						
30-day only	9,362	0.65	0.60–0.70	<0.001	8.33	8.31–8.36
Combination	6,083	0.37	0.32–0.42	<0.001	8.05	8.03–8.08
90-day only	1,280	Reference			7.69	7.64–7.73
Age <20 years						
Duration of prescription						
30-day only	1,346	0.62	0.43–0.81	<0.001	8.95	8.87–9.02
Combination	1,018	0.37	0.18–0.57	<0.001	8.71	8.63–8.78
90-day only	112	Reference			8.33	8.16–8.51
Age ≥20 years						
Duration of prescription						
30-day	8,016	0.62	0.57–0.67	<0.001	8.26	8.23–8.28
Combination	5,065	0.32	0.27–0.37	<0.001	7.96	7.93–7.98
90-day	1,168	Reference			7.64	7.59–7.68
Female						
Duration of prescription						
30-day	4,384	0.63	0.55–0.70	<0.001	8.36	8.32–8.39
Combination	2,843	0.36	0.29–0.44	<0.001	8.09	8.05–8.13
90-day	622	Reference			7.73	7.67–7.80
Male						
Duration of prescription						
30-day	4,978	0.67	0.60–0.74	<0.001	8.31	8.28–8.34
Combination	3,240	0.37	0.30–0.44	<0.001	8.02	7.98–8.05
90-day	658	Reference			7.64	7.58–7.70

was initially diagnosed. We limited eligibility to children and adults of working age (0–64 years of age).

Cohort Study: Between-Patient Comparison

The first design was a cohort study comparing A1C values in patients who received *1*) 30-day prescriptions, *2*) 90-day prescriptions, and *3*) a combination of 30- and 90-day prescriptions. Generalized estimating equations (GEEs), which account for repeated measures within patients, were used, incorporating the Gaussian family, identity link, and exchangeable correlation structure (with robust estimates of variance). Prescription duration was regressed on A1C (dependent variable) with $\alpha = 0.05$ (two-tailed). Results were stratified by age, sex, and whether the medication was mailed to the patient (versus picked up from a pharmacy). The resulting coefficient indicates the degree to which the mean A1C changed from a 30-day-only prescription compared to a 90-day-only prescription (reference group). A positive coefficient indicates a greater mean A1C value in the 30-day group relative to the 90-day group. A negative coefficient indicates an inverse association. In secondary analyses, we included an interaction term for region of the country and season of the year. Analyses were conducted using Stata/MP 15.1 (StataCorp., College Station, Tex.).

Self-Controlled Case Series: Within-Patient Comparison

For the second study, a self-controlled case series design was used, in which A1C values were compared within the same person (5). Subjects were patients who switched between 30- and 90-day prescriptions. We compared A1C levels after 30-day insulin prescriptions to A1C levels after 90-day insulin prescriptions. Each patient was required to have, at minimum, three 30-day supplies (covering a 90-day period) and, at minimum, one 90-day supply (covering a 90-day period). To ensure a similar exposure, we limited eligibility to patients using rapid-acting insulins (i.e., insulin lispro, insulin aspart, or insulin glulisine) of equal concentration (100 units/mL).

For the self-controlled case series design, a linear fixed effects model was used, accounting for the repeated measures within the same patient (5). Duration of supply (30 days vs. 90 days) was the primary explanatory variable and was regressed on A1C (dependent variable) with adjustment for age. The α was set at 0.05 (two-tailed). Analyses were again conducted using Stata/MP 15.1.

Results

Cohort Study: Between-Patient Comparison

In the cohort study, there were 16,725 eligible patients (9,362 with 30-day, 1,280 with 90-day, and 6,083 with both 30- and 90-day prescriptions). A total of 7,849 patients were female (46.9%), with no difference in sex across the three prescription types ($P = 0.460$). The mean age of patients was 38.2 years (SD 15.4 years), and the median age was 39 years (IQR = 26–51). Patients had an average of 3.1 A1C tests. Patients who used 30-day prescriptions had a mean A1C value 0.65 percentage points greater than those who used 90-day prescriptions ($P < 0.001$) (Table 1). That is, the mean A1C was 8.33% in patients with 30-day prescriptions versus 7.69% in patients with 90-day prescriptions, for a 0.65 percentage-point difference in A1C (with rounding). Patients who used a combination of 30- and 90-day prescriptions had a mean A1C value of 8.05%, which was intermediary between that of patients with 30-day and 90-day prescriptions.

Results were similar when stratified by age (Table 1). For those <20 years of age, mean A1C values were 8.95% for 30-day, 8.71% for combination, and 8.33% for 90-day prescriptions. For those ≥20 years of age, the mean values were 8.26, 7.96, and 7.64%, respectively. Patterns were similar when stratified by sex (Table 1).

Mailed prescriptions were associated with lower A1C ($P < 0.001$). Mean A1C was 7.58% (95% CI 7.53–7.63%) when all prescriptions were mailed and 8.21% (95% CI 8.19–8.23%) when not. After simultaneous adjustment for age, sex, duration of supply, and mailed status in the GEE model, both 90-day prescriptions and mailed prescriptions were independently associated with lower A1C values ($P < 0.001$ for both). Mean A1C values and 95% CIs are shown in Figure 1, illustrating the difference between mailed versus pharmacy (pick-up)

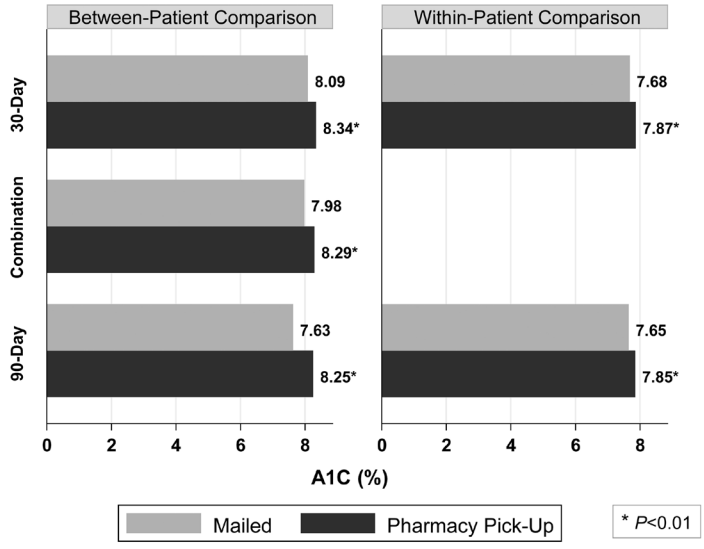

FIGURE 1. Mean A1C by duration of insulin prescription and type of prescription delivery.

TABLE 2. A1C by Duration of Insulin Prescription: Within-Patient Comparison

		A1C			Predicted A1C, %	
Variables	***n***	**Mean Change**	**95% CI**	***P***	**Mean**	**95% CI**
Overall						
Duration of prescription						
30-day	1,712	0.175	0.121–0.228	<0.001	7.87	7.83–7.90
90-day		Reference			7.69	7.65–7.73
Age <20 years						
Duration of prescription						
30-day	176	–0.004	–0.227 to 0.219	0.0972	8.62	8.47–8.77
90-day		Reference			8.63	8.47–8.78
Age ≥20 years						
Duration of prescription						
30-day	1,536	0.203	0.150–0.256	<0.001	7.79	7.76–7.83
90-day		Reference			7.59	7.55–7.63
Female						
Duration of prescription						
30-day	841	0.131	0.054–0.207	<0.001	7.85	7.80–7.90
90-day		Reference			7.72	7.67–7.77
Male						
Duration of prescription						
30-day	871	0.225	0.150–0.300	<0.001	7.88	7.83–7.93
90-day		Reference			7.66	7.61–7.71

prescriptions when stratified by the duration of the prescription. Mailed 90-day insulin prescriptions exhibited the lowest mean A1C.

A1C values were not significantly elevated when mailed prescriptions were filled in the winter in the northern region of the country compared to the spring, summer, or autumn (P = 0.264 for the interaction between season and northern region). Likewise, A1C values were not significantly elevated when mailed prescriptions were filled in the summer in the southern region of the country compared to other seasons (P = 0.815 for the interaction between season and southern region).

Self-Controlled Case Series: Within-Patient Comparison

There were 1,712 patients with type 1 diabetes who had filled both 30- and 90-day insulin prescriptions. Approximately half (49.1%) were female, and 50.9% were male. The mean age was 39.6 years (SD 14.2 years). The 1,712 patients were observed under private health insurance coverage for an average of 6.6 years (95% CI 6.4–6.7 years).

Overall, there were 11,403 A1C measurements in this cohort, with an average of 6.7 values per patient. Mean A1C values were 0.175 percentage points greater after 30-day insulin prescriptions than after 90-day prescriptions (P <0.001) (Table 2). That is, mean A1C values were 7.87% after the 30-day prescriptions and 7.69% after the 90-day prescriptions (for a difference of 0.18 percentage point, with rounding).

Results were stratified by age (Table 2). For those <20 years of age, there was no significant difference in A1C values based on duration of supply; the mean A1C values were 8.62% after 30-day prescriptions and 8.63% after 90-day prescriptions (P = 0.972). For those ≥20 years of age, however, the results were statistically significant. Mean A1C was 7.79% after 30-day supplies and 7.59% after 90-day supplies (P <0.001).

In females, A1C values were 0.131 percentage point greater after 30-day insulin prescriptions than after 90-day prescriptions (P = 0.001) (Table 2). The results were similar in males, with greater mean A1C values after 30-day supplies (7.88%) than after 90-day supplies (7.66%).

There were 4,627 mailed insulin prescriptions and 6,768 with pharmacy pick-up. Mailed prescriptions were associated with lower A1C values

than those picked up at a pharmacy (P <0.001). Mean A1C was 7.65% with mailed prescriptions (95% CI 7.61–7.69%) and 7.87% with pharmacy pick-up prescriptions (95% CI 7.83–7.90%). Of the mailed prescriptions, 95.8% were 90-day supplies.

In secondary analyses, we found that mean A1C values were not significantly different when mailed prescriptions were filled in the winter in the northern region of the United States compared to other seasons of the year (P = 0.732). Likewise, mean A1C values were not significantly different when mailed prescriptions were filled in the summer in the southern region of the United States compared to other seasons (P = 0.591).

Discussion

In this nationwide study, 90-day insulin prescriptions were associated with lower A1C values than 30-day prescriptions. This held true for both sexes and in adults. Although these results were statistically significant, the clinical difference in A1C values was modest. There was no significant difference between A1C values by duration of prescription in youth when using the within-person comparison. This could be due to the smaller number of patients who were <20 years of age (n = 176) who had switched between 30- and 90-day prescriptions. Most of the youth in this nationwide sample used 30-day prescriptions for rapid-acting insulins. The number of patients receiving only 30-day prescriptions (n = 9,362) was considerably greater than the number of patients receiving only 90-day prescriptions (n = 1,280), which is a reflection of practices during the study period (2001–2015). This did not, however, hamper the ability to detect a difference in A1C values overall.

In addition, we found no evidence of higher A1C levels when the prescriptions were mailed during winters in the north or during summers in the south, which may alleviate some concerns regarding integrity of the product during shipment. Chandler et al. (6) evaluated the integrity of various insulins after simulated packaging and delivery conditions and found that the products maintained their stability, although the number of samples tested was small.

In a recent systematic review and economic assessment of shorter (28-day) versus longer (3-month) durations of drug prescriptions, the authors found that, for patients with chronic conditions, longer prescription lengths yielded more cost savings (after balancing medication waste, dispensing fees, and prescriber time) (7). Although most of the studies in the review evaluated oral medications, Murphy et al. (8) assessed 30- versus 90-day insulin prescriptions and found, after adjustment for age, sex, and type of insulin, no difference in wastage by duration of prescription (8). We add to this literature by assessing an essential clinical outcome of glycemic control. This is of considerable importance for patients with type 1 diabetes because mortality risk increases with levels of A1C, reported at 7.01/1,000 patient-years with A1C of ≤6.9%, which increases to 16.25/1,000 patient-years with A1C of ≥9.7% (9).

Although the underlying reason why 90-day prescriptions may be associated with lower A1C in adults is unknown, interruptions in health insurance for working-age adults with type 1 diabetes are fairly common. It has been shown that one in four working-age adults with type 1 diabetes experience at least one interruption in health insurance coverage over an average of 2.6 years (10). Interruptions of 31–270 days in health insurance are associated with a fivefold increase in hospitalizations and use of acute care services in adults with type 1 diabetes (10). Thus, a longer prescription duration may assist with extending the availability of insulin during these gaps in coverage.

A limitation of this investigation is its observational nature. We cannot rule out the influence of other factors that may affect glycemic control. However, in our study, confounding by interpersonal differences was minimized because we included a comparison within the same person. Additionally, because there was no study recruitment, it is unlikely that the results were due to volunteer bias. In the self-controlled case series, the type of insulin was held constant so that the findings were not due to receiving different types or concentrations of insulin.

Conclusion

A1C levels in adults with type 1 diabetes were significantly lower with 90-day insulin prescriptions than with 30-day prescriptions, although the clinical difference in mean A1C values was modest. Because the risks of cardiovascular, renal, ophthalmic, and neurological complications increase with A1C levels (11,12) and because the use of insulin is the preeminent factor affecting A1C in patients with type 1 diabetes (13), it is possible that prescriptions of longer duration may provide less disrupted access to insulin for some patients. Mailed, 90-day insulin prescriptions may be a reasonable choice for adult patients with stable type 1 diabetes.

Duality of Interest

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

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Author Contributions

M.A.M.R. designed the study and, with J.M.L., obtained funding and secured the use of the database. T.B. extracted the files from the larger database and, with M.A.M.R., analyzed the data. All authors participated in writing the manuscript, reviewing the literature, and interpreting the results. All authors critically reviewed and approved the final version of the manuscript. M.A.M.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the

integrity of the data and the accuracy of the data analysis.

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