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ORIGINAL REPORT

Refill compliance in type 2 diabetes mellitus: a predictor of switching to insulin therapy?

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SUMMARY

Objective To assess whether switching to insulin therapy in patients with type 2 diabetes mellitus is associated with medication refill compliance of oral hypoglycemic agents.

Research Design and Methods The PHARMO Record Linkage System was used as data source for this study. Patients with newly treated type 2 diabetes mellitus were defined as subjects in whom oral hypoglycemic therapy was initiated between 1991 and 1998. We performed a matched case-control study in this cohort. Cases were patients who switched to insulin therapy. Date of switching in the case was defined as the index date. Controls were subjects still on oral therapy on the index date, matched on duration of diabetes and calendar time. We measured the medication refill compliance in the year starting 18 months before the index date and calculated various compliance indices.

Results In total, 411 cases and 411 matched controls were identified. Cases suffered more often from more severe comorbidity and used a higher number of oral hypoglycemic agents and concomitant non-diabetic drugs. The overall compliance rate did not differ significantly between cases and controls, the adjusted odds ratio (OR) was 1.3 (CI 95% 0.6–2.8). After performing multivariate logistic regression modeling, age at onset of diabetes, gender, comedication, combination therapy, and daily dosage frequency, were independently related to switching.

Conclusions We were unable to confirm the hypothesis that noncompliance with treatment is more prevalent in patients with secondary failure. Other variables, like comorbidity and disease-related factors seem to play a more important role in switching to insulin therapy. Copyright © 2002 John Wiley & Sons, Ltd.

KEY WORDS — type 2 diabetes mellitus; insulin; refill compliance; oral hypoglycemic agents

INTRODUCTION

Oral hypoglycemic agents are the major treatment for people with type 2 diabetes mellitus. As type 2 diabetes mellitus advances, secondary failure of oral hypoglycemic therapy develops as a consequence of progressive loss of β-cell function and worsening of insulin resistance caused by persistent hyperglycemia and possible development of drug resistance.[1,2] Each of the available oral hypoglycemic agents has limited glucose-lowering efficacy and many patients eventually require insulin to avoid marked hyperglycemia.[3] Furthermore, other factors, such as severity of the disease itself and younger age at diagnosis, may contribute to disease exacerbations leading to a switch to insulin therapy due to secondary failure.[4,5]

Noncompliance with prescribed regimens is one of the main causes of poor metabolic control in patients with diabetes.[6] An estimated 10–30% of patients with

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type 2 diabetes withdraw from their prescribed regimen within 1 year of diagnosis and, of the remainder, nearly 20% administer insufficient medication to facilitate an adequate reduction in blood glucose.[7] 'Compliance' has been defined as an attempt by patients to take their medication each day as prescribed, or the extent to which the patient's actual history of drug administration corresponds to the prescribed regimen.[8] Patients typically take less medication than they have been prescribed. In several studies assessing adherence to glucose lowering regimens, overall compliance rates between 64 and 83% were found for oral hypoglycemic agents.[9–12]

The prescription refill records of centralized pharmacies are a potential source of information about patient compliance. Based on the assumption that a patient cannot be compliant when he has not obtained sufficient medications, *refill compliance* can be measured.[13] Population-based studies of refill compliance showed that many, if not most, patients fail to continue medication intended for long-term use;[14] therapy discontinuation rates for oral hypoglycemic agents varied between 8 and 16% per year.[10,15]

Noncompliance of oral hypoglycemic agents results in decreased glycemic control, which falsely indicates secondary failure and unjustified initiation of insulin therapy. The purpose of the present study was to assess whether switching to insulin therapy in patients with type 2 diabetes is associated with medication refill compliance of oral hypoglycemic agents.

PATIENTS AND METHODS

Data source

The PHARMO Record Linkage System (PHARMO RLS) was used as data source for this study. The PHARMO RLS comprises pharmacy dispensing records linked to hospital discharge data of all community-dwelling residents of eight Dutch cities, counting for more than 450 000 patients histories, from 1985 onwards.[16,17] Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification.[18] Because in the Dutch health care system patients are usually designated a single pharmacy to fill their prescriptions independent of prescriber, virtual complete data are available for each subject. These data include sex, date of birth, drug names with ATC codes, dispensing date, total supply, prescribed dosage regimen, prescriber, dates on admission and discharge from hospital, and discharge diagnoses.

Study subjects

Patients with newly treated type 2 diabetes mellitus were defined as subjects in whom oral hypoglycemic therapy was initiated between 1991 and 1998. The date of starting oral hypoglycemic treatment was presumed to approximate their date of clinical diagnosis. Patients were eligible for inclusion in the cohort if they received no hypoglycemic medication during 180 days (half a year) preceding the date of starting oral hypoglycemic agent use. Furthermore, patients were only included if they were dispensed at least two consecutive prescriptions of oral hypoglycemic agents.

We performed a matched case-control study, nested in this cohort of patients with type 2 diabetes. Cases were patients initially treated with oral hypoglycemic agents who added or switched to insulin therapy. Date of switching in the case was defined as the index date for each matched pair. Their medication history of oral hypoglycemic therapy before the switch was at least 18 months. Controls were subjects still on oral therapy on the index date. We matched cases and a similar number of controls on calendar time (quarter of the year) of first prescription of an oral hypoglycemic agent. From the 430 cases who met the inclusion criteria, 16 were excluded because they discontinued their oral therapy in the 18-month period before the index date. Discontinuation of pharmacotherapy was defined as a gap of at least 365 days (a year) during which the patient used no hypoglycemic agents at all. For three cases, the matching procedure was not successful. Eventually, these additional exclusions left 411 cases and 411 controls for study.

Medication use

In general, Dutch pharmacy policy limits the quantity of medications dispensed at one time to a 3-month supply and requires physicians to write new prescriptions at six-month intervals. All prescriptions for oral hypoglycemic agents (sulfonylureas, biguanides, or alpha-glucosidase inhibitors) were retrieved. Both for the cases and controls, we measured the medication refill compliance in the year starting 18 months (a year and a half) before the index date (called 'risk window'), excluding the half-year period before the index date. Visualized:

The reason we disregarded this 'black period' is because we knew from clinical practice that this episode just before a switch to insulin is frequently featured by cluttered and erratic drug use patterns, with several oral hypoglycemic agents prescribed at the same time and often an unclear dosage regimen, due to the lack of adequate glycemic control in this period. With regard to drug regimen characteristics and complexity, three variables were created from the prescription profile of each patient: the average number of doses per day of oral hypoglycemic agents, presence of combination therapy (concomitant use of more than one hypoglycemic agent), and the number of concurrent medications other than hypoglycemic drugs.

Ascertainment of refill compliance

The pharmacy data were used to calculate the compliance measure on the basis of an index previously developed and validated by Steiner *et al*.[13] The intended duration of every oral hypoglycemic agent prescription was calculated from details on the dispensing (total amount dispensed and drug regimen). Firstly, we calculated MED_INT (Medication-Interval) for all successive prescriptions during the exposure window. MED_INT is the ratio of days' supply obtained at the beginning of a specific time interval to the days elapsed before the subsequent refill. For a series of refill intervals, an overall measure of compliance, MED_TOT (Medication-Total), was calculated as the total supply of pills dispensed divided by the total number of days elapsed. Because measures of medication availability may fail to identify clinically meaningful treatment gaps, we also used a third compliance index, MED_OUT (Medication-Out). MED_OUT was defined as the total number of days without medications divided by the total days of observation. So, if it comes to perfect compliance, i.e. continuous drug availability, MED_TOT = 1 and MED_OUT = 0.

Subsequently, different categories of compliance were created from these continuous indices. A classification of undercompliance ('gap') was given if the patient refilled the prescription more than 7 days after the expected date or MED_INT was $<90\%$. A classification of overcompliance ('oversupply') was given if the patient refilled the prescription more than 7 days before the expected date or MED_INT was $>110\%$. Relative over- and undercompliance was assessed by dividing the total number of oversupplies and gaps, respectively, by the total number of dispensings. Furthermore, we looked at compliance as a dichotomous measure and considered patients to be sufficiently compliant with their treatment when at least 80% of the days in the study period were covered.[19,20] Since the outpatient pharmacies do not record prescriptions dispensed during an inpatient admission, the number of days spent in the hospital was included in the model to control for possible underestimation of compliance due to hospitalizations.

Comorbidity

An individual's morbidity and overall health status was assessed using the chronic disease score (CDS), a validated measure of chronic medical conditions based on medications used.[21–23] The CDS was calculated by assigning scores (0–5) to classes of drugs according to the severity of the disease for which they were prescribed during a 1-year period, the (hypothetical) maximum total score being 35. Because the study population comprised patients with type 2 diabetes mellitus, the minimum score was 2. For example, a CDS of 7 or more is associated with a fivefold increase in the risk of hospitalization and a tenfold increase in the risk of death.[21]

Statistical analysis

We performed conditional logistic regression analysis to estimate matched odds ratios (ORs) with respect to the different compliance indices for cases compared to controls, and 95% confidence intervals (CIs), using EGRET.[24] With regard to potential confounding, we controlled for age, sex, drugs regimen characteristics, days of hospitalizations, and comorbidity as measured by the chronic disease score. We used Chi-square (categorical variables) and Mann–Whitney (continuous variables) tests to evaluate differences in general characteristics between cases and controls. Furthermore, we performed multivariate conditional logistic regression analysis to define a model including only strong and/or known predictors of switching to insulin therapy.

RESULTS

In this nested case-control study, 411 cases (patients who switched to insulin) and 411 matched controls (those who did not switch) were identified in the period from 1991 to 1998. General characteristics are given in Table 1. There was a borderline significant difference with respect to sex distribution in cases and controls (50% vs. 44% males, respectively, $p = 0.06$). The mean chronic disease score, as an

Table 1. General characteristics of the study population

Variable	Cases ($N=411$)	Controls ($N=411$)	p-value
Male sex (%)	207 (50%)	180 (44%)	0.059
Age at onset*(yrs)	59.0 ± 0.6	65.0 ± 0.6	<0.001
Calendar year of onset*	1993.9 ± 0.07	1993.9 ± 0.07	...
Duration of disease† (yrs)	3.5 ± 0.07	3.5 ± 0.07	...
Age at switching (yrs)	62.5 ± 0.6	...	...
Chronic disease score:			
2	95 (23%)	105 (26%)	0.416
3–5	110 (27%)	120 (29%)	0.437
6–7	93 (23%)	113 (27%)	0.107
>7	113 (28%)	73 (18%)	0.001
Comedication (total number of drugs)‡	8.3 ± 0.3	7.0 ± 0.2	0.004
Number of hospitalizations‡			
0	351 (85%)	359 (87%)	0.416
1	40 (10%)	41 (10%)	0.907
≥2	20 (5%)	11 (3%)	0.099
Drug regimen			
1. Monotherapy	172 (41.8%)	291 (70.8%)	<0.001
OHA§			
Tolbutamide	34.9	50.9	0.001
Glibenclamide	37.8	22.7	<0.001
Gliclazide	18.0	19.6	0.678
Glimepiride	4.1	0.3	0.003
Metformin	5.2	5.5	0.903
Acarbose	0	1.0	0.182
2. Combination therapy	239 (58.2%)	120 (29.2%)	<0.001
Number of OHAs§	1.8 (1–4)	1.3 (1–3)	<0.001
Daily dosage frequency	2.1 (1.0–3.7)	1.9 (1.0–4.0)	<0.001

Data are means ± SEM or number; variance or percentages between parentheses.
*Date of first prescription of oral hypoglycemic agent.
†At indexdate, i.e. date of switching to insulin therapy of the cases.
‡During the one year period refill compliance was measured.
§Oral hypoglycemic agent, with respect to use of OHAs, percentages are given.

indicator of morbidity and overall health status, was not different in cases and controls (5.7 vs. 5.3, $p = 0.07$). Severe (co)morbidity (CDS > 7) was more prevalent in cases compared to controls (28% vs. 18%, $p = 0.001$). In total, 112 (13.6%) patients were hospitalized during the 1-year exposure period, the maximum number of hospitalizations was 6. With respect to concomitant drug use, cases used on average one (not hypoglycemic) drug more than controls ($p = 0.004$). Cases were about twice more likely to use more than one hypoglycemic agent; 239 (58%) cases received combination therapy, compared to 120 (29%) of the controls ($p < 0.001$). The most common combination was a second-generation sulfonylurea derivative with metformin (59%), followed by two different sulfonylureas (16%) and a second-generation sulfonylurea with acarbose (12%).

Table 2 presents various ascertained compliance indices in cases and controls. The overall compliance rate (MED_TOT) and MED_OUT did not differ

Table 2. Compliance indices in cases and controls

Outcome variable	Cases ($N=411$)	Controls ($N=411$)
Compliance rate (MED_TOT)	0.98 (0.17–2.39)	0.96 (0.24–1.55)
Compliance category*		
<0.70	9.2	10.0
0.70–0.89	16.3	16.5
0.90–1.10	51.6	58.4
1.11–1.30	18.2	10.7
>1.30	4.6	4.4
MED_OUT	0.15 (0–0.86)	0.14 (0–0.76)

Variance or percentages between parentheses.
*With respect to compliance categories, percentages are given.

Table 3. Determinants of switching to insulin therapy*

Variable	OR	CI95%
Gender (1 = male)	1.45	1.04–2.03
Age at onset (per year)	0.96	0.94–0.97
Comedication (per extra drug)†	1.08	1.04–1.11
Glucose lowering combination therapy (1 = years)	3.44	2.36–5.03
Daily dosage frequency	1.34	1.03–1.74
Undercompliance‡	1.07	0.72–1.57
Overcompliance‡	1.51	0.96–2.36

*Multivariate conditional logistic regression modeling.
†number of drugs besides hypoglycemic medication.
‡Undercompliance: overall compliance rate <90%; overcompliance: overall compliance rate. >110%; Reference category: overall compliance rate 90–110%.

significantly between cases and controls. The crude OR for MED_TOT was 1.5 (CI 95% 0.8–2.8). In addition, after controlling for comorbidity (CDS, hospitalizations), drug regimen characteristics (dosage frequency, combination of oral hypoglycemic therapy, concurrent medication), and patient characteristics (gender, age at onset), the adjusted OR was 1.3 (CI 95% 0.6–2.8). With respect to the different oral hypoglycemic agents, mean compliance rates varied between 96.2 (glimepiride) and 99.3% (acarbose). Compliance was related to frequency of dosage and varied between 98.1 (once or twice daily) and 93.6% (three or more times daily), $p = 0.01$.

When we considered patients sufficiently compliant with an overall compliance rate of at least 80%, 86.1% of the cases and 83.5% of the controls were compliant, this difference was statistically not significant ($p = 0.29$). Relative overcompliance was more prevalent in cases (32% vs. 28%, resp.) with a matched OR of 1.9 (CI 95% 1.0–3.7). With respect to relative undercompliance, cases and controls were comparable (33% vs. 34%, resp.). When compliance was defined as 1-MED_OUT, mean compliance was $85.3 \pm 15\%$.

As presented in Table 3, the following variables were related to switching: gender, age at onset of diabetes, comedication, combination therapy (simultaneous use of more than one oral hypoglycemic agent), daily dosage frequency. Overcompliance, defined as a mean overall compliance rate higher than 110%, was a borderline significant determinant ($p = 0.07$).

DISCUSSION

We measured refill compliance with oral hypoglycemic therapy among patients who switched to insulin therapy and those who did not. The finding that compliance was only borderline associated with switching does not support the hypothesis that noncompliance with treatment is more prevalent in patients with secondary failure. A recent study by Evans *et al.* for the DARTS/MEMO collaboration showed similar results; they found in a comparable diabetic population even significantly improved compliance in patients who did commence insulin (100.4% vs. 92.9% in non-switchers, $p < 0.001$).[25] Other variables, like patient and drug regimen characteristics seem to play an important role in explaining switching to insulin therapy.

Pharmacy records provide a reliable tool to measure drug exposure when compared with home inventory (e.g. a comparison between the prescribed medication vs. the medication in the patient's home) or pill count.[9,26] One important advantage is avoidance of any Hawthorne effect (i.e. improvement of performance when the subject is under observation) by assessing compliance retrospectively by review of prescription-refill records.[27]

Furthermore, it is known that observational studies of drug exposure can be more accurately estimated from dispensing rather than prescribing data, for example, Beardon *et al.* found an overall rate of non-redemption of 5.2% with regard to prescriptions.[28] Paes and his colleagues already proposed that the use of refill data might be especially useful in the community pharmacy setting.[9] One advantage of this method is that pharmacy computers can deliver a signal if the patient is too late for his or her refill.[7] It provides the possibility to monitor a large number of patients without extra investments.

Compared to similar studies, we found a reasonably high overall compliance rate of 97%.[9,10,12,30] For example, Paes *et al.* examined the compliance as registered by MEMS® (Medication Event Monitoring System) devices of a group type 2 diabetes mellitus patients.[12] They excluded patients using a weekly dose organizer (a substantial part in an elderly population). They found an overall compliance of 74.8%, but compliance was strongly related to frequency of dosage and varied between 98% (once daily) and 66% (three-times daily). We found that higher complexity of the dosage regimen (more comedication, use of combination therapy and higher number of dosages per day) was also associated with a higher risk of switching. This finding supports the 'stepping stone theory', intrinsic to secondary failure. Before the ultimate switch to insulin, intermediate steps are taken, like raising the doses and addition of other oral hypoglycemic agents due to gradually worsening of metabolic control. When we defined compliance as

1-MED_OUT, our results were compatible with a study by Venturini,[11] mean compliance rates were 85% and 83%, respectively.

Refill compliance measures, however, have inherent limitations. First, and most important, refill compliance measures cannot assess the relationship between the duration of drug action and the timing of doses, which has a critical impact on the efficacy of treatment in diabetes. Studies with reliable compliance assessment have shown that the main error patients make is to take the prescribed dose at longer-than-prescribed intervals—often by hours.[29] Other cons of this method are that nothing can be said about patients getting their refills on time, the cause of noncompliance is unknown and in general the results will overestimate compliance.[9] For instance, it is quite common to cash a repeat prescription several days before it is needed for reasons of convenience. However, the occurrence of this phenomenon is not expected to be different between cases and controls. Besides that, measures of treatment gaps make the assumption that both embedded and terminal gaps are due to noncompliance by the patient rather than drug discontinuation by the clinician. Unfortunately, the computerized pharmacy records only provide information on the dosage regimen at the time the prescription is filled, interim changes by the physician remain unobserved. The fact that we did not reveal any difference in compliance rates between cases and controls could be due to interim changes to the drug regimen. Cases are more likely to receive increasing doses in response to their poor glycemic control, resulting in an overestimation of the compliance rate. It is important to realize that if the daily dose changes, so does the duration of supply on hand. For example, if a patient were instructed to double his daily dose, his residual days' supply would be halved. Hence, the refill compliance measurement would be an overestimation of reality. After all, relative overcompliance was substantially higher in the cases. Nevertheless, the high specificity of refill compliance allows identification of a subset of individuals who cannot be taking enough medication to attain a treatment goal, because they have not obtained enough drugs in the pharmacy.[14]

Within the diabetes literature, the tendency has been to treat adherence and metabolic control as interchangeable constructs.[6,31] Adherence is one factor, but not the only factor, which may influence a patient's metabolic status only when an effective treatment regimen has been prescribed by the physician.[6] Although early addition of other agents may delay the increasing hyperglycemia, each of the available oral hypoglycemic agents has limited glucose-lowering efficacy and many patients eventually require insulin to avoid marked hyperglycemia (i.e. secondary failure). In the UK Prospective Diabetes Study (UKPDS), the worsening of glycemic control has been attributed to the natural course of type 2 diabetes and lack of efficacy of current antihyperglycemic therapy.[3] We showed that besides adherence, other, sometimes unchangeable, factors (e.g. age and gender) are strong predictors of switching to insulin therapy.

In conclusion, we found that noncompliance in general was not associated with switching to insulin in type 2 diabetic patients. In the near future, it could be useful to explore the relationship between 'timing compliance' (timing of doses) and metabolic control using the MEMS® method. We suggest that other factors independent of a patient's willingness to adhere to a treatment regimen, like disease-related factors, are more relevant in explaining secondary failure in most patients.

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