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ORIGINAL ARTICLE

Multicentre Evaluation of Adherence to Extended-Release Metformin in Daily Practice in Russia

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Abstract

Objective: We conducted a multicentre, observational, non-interventional evaluation of adherence (by tablet counting) to an Extended-Release (XR) metformin preparation (Glucophage® XR) as antidiabetic monotherapy in 201 patients with type 2 diabetes in the routine care setting.

Research design and methods: Patients had previously received immediate-release metformin for at least 8 weeks, followed by metformin XR for at least 4 weeks. The duration of follow-up was 6 months.

Main outcome measures: Adherence to therapy and patient's preferences for extended-release vs. immediate release formulations.

Results: Adherence to metformin XR was "excellent" (> 90%) in 194 patients (96.5%) and "good" (> 75%) in the remaining 7 patients (3.5%). Almost all patients (194/201; 96.5%) expressed a preference for metformin XR compared with immediate-release metformin, 6 patients preferred immediate-release metformin (3.0%) and the remaining patient (0.5%) expressed no preference. Greater convenience of treatment was the most common reason driving patient preference for a regimen (cited by 88.6% of the overall population). Fasting blood glucose was high (according to local laboratory reference ranges) in 57% of patients at baseline and 42% at study end; corresponding percentages for elevated HbA1c were 48% and 43%, respectively. Metformin XR was well tolerated.

Conclusions: This population of type 2 diabetes patients managed in the usual care setting adhered well to an extended-release metformin regimen, with strong preference overall for this regimen over their previous immediate-release metformin regimen.

Keywords

Adherence, Type 2 diabetes, Extended-release metformin, Real world data

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Introduction

Major guidelines support the use of metformin for the initiation of pharmacologic antihyperglycaemic therapy within the management of type 2 diabetes [1-4]. Metformin is available as a standard, immediate-release formulation (usually taken two or three times daily) and also in an extended-release (XR) formulation (designed to be taken once-daily).

The first marketing authorisation for metformin immediate-release was granted in France in March 1959. The extended-release formulation was first authorised in the UK on 26th November 2004. Currently, both formulations are being marketed in over 150 countries around the world.

Glucophage SR 500 mg Prolonged Release tablet, same as extended release (XR), (PL 116748/0054) has been authorised in the UK on 26th November 2004; Glucophage SR 750 mg Prolonged Release Tablet (PL 11648/0066) has been authorised in the UK on 21st February 2008, and Glucophage SR 1000 mg Prolonged Release Tablet (PL 11648/0067) has been authorised in the UK on 16th September 2008. Glucophage 500 mg film-coated tablets were first authorised in the UK in 21st September 1982 by Lipha Pharmaceutical Ltd.

Pharmacokinetic analysis shows that the XR formulation smooths the delivery of metformin into the blood stream over the 24 hour dosing interval, while not affecting overall exposure to metformin (Area Under The Plasma Concentration-Time Curve [AUC]), compared with the same daily dose of twice daily-immediate release metformin [5]. Once-daily formulations have been shown to provide greater convenience for patients, supporting better adherence to the antidiabetic regimen, compared with treatments that need to be taken multiple times per day [6]. Metformin XR may also support better tolerability compared with the immediate-release version [3]. It is important to note that the vast majority of patients are not managed within a clinical trial and it is important to study adherence to therapies within an ambulatory setting. We evaluated adherence to a metformin XR (Glucophage XR, Merck) administered as part of routine care in a population of type 2 diabetes patients in a multicentre, non-interventional observational study in ten centres in the Russian Federation.

Patients and Methods

Objectives of the study

The primary endpoint of the study was to evaluate the adherence rate to metformin XR in daily practice. Categories of adherence were defined *a priori* as "excellent" (> 90%), "good" (75-90%), "moderate" (50-75%) or "poor" (< 50%). Secondary objectives were to evaluate:

- The level of glycaemic control (HbA1c, Fasting Blood Glucose [FBG]);
- Safety and tolerability: Adverse Events (AE) and Adverse Drug Reactions (ADRs), using Medical Dictionary for Regulatory Activities (MedDRA) coding and rated by study Investigators for association with study treatment and for severity using the Qualitative Toxicity Scale;
- The preference of the subjects for metformin XR vs. the immediate-release formulation of metformin.

Patients

Patients eligible for the study were adults (≥ 18 years of age) with type 2 diabetes, who had received previous treatment with immediate-release metformin for at least 8 weeks. Key exclusion criteria were pregnancy or lactation (female participants used a reliable method of contraception), contraindications to metformin according to local labelling, receipt of any other antihyperglycaemic medication, participation in another clinical trial within 30 days before the start of the study, or significant illness likely to interfere with the conduct of the study.

Study design

This was a non-interventional, non-randomised, uncontrolled, single-arm study carried out in ten centres in the Russian Federation. Patients had been switched from immediate-release metformin to once-daily metformin XR at a similar daily dose for at least four weeks before the start of the study and followed for 6 months. Changes in the dose of metformin XR were permitted as required to maintain optimal diabetes management in the opinion of the physician. Adherence was evaluated using tablet counting, supported by patient diaries, where used.

Statistical analysis was conducted using Statistical Analysis System (SAS) version 9.1.3 (NC, USA). All subjects enrolled in to the study and who received at least one dose of study treatment were analysed for efficacy and safety.

Results

Patients

A total of 204 patients were screened, of whom 201 received treatment and were analysed. Patients were predominantly female, obese on average, and had a relatively short duration of diagnosed diabetes of about 3 years (Table 1). Most were non-smokers with moderate alcohol consumption; more than two-thirds had concomitant cardiovascular disease and about one-third had concomitant hepatic disease (Table 2). The prior duration of treatment with immediate-release metformin was about 2 years on average, with almost all patients receiving twice-daily treatment (Table 3). Patients had taken metformin XR for an average of 21 months at the start of the follow-up period. The mean final dose of metformin XR (1275 ± 447 mg) was similar to the

Table 1: Patient characteristics at baseline.

Male/female n (%)	53 (26)/148 (74)
Age (y)	
N (%)	201 (100)
Missing (%)	0
Mean (SD)	59.7 (10.2)
Median	61
Q1; Q3	54.0; 66.0
Range	29-85
Weight (kg)	
N (%)	201 (100)
Missing (%)	0
Mean (SD)	88.2 (18.3)
Median	84
Q1; Q3	76.0; 98.0
Range	51-175
Height (cm)	201 (100)
Missing (%)	0
Mean (SD)	165.6 (8.7)
Median	164
Q1; Q3	159.0; 172.0
Range	148-188
Body mass index (kg/m²)	201 (100)
Missing (%)	0
Mean (SD)	32.1 (5.7)
Median	31.2
Q1; Q3	28.3; 34.9
Range	21.8-62

Table 2: Patient history at baseline.

Smoking history, n (%)	201 (100)
Smoker	17 (8.4)
Ex-smoker	16 (8)
Non-smoker	168 (83.6)
Alcohol use, n (%)	201 (100)
Once per week	144 (71.6)
2-4 times per week	3 (1.5)
≥ 5 times per week	0
None	44 (26.9)
Concomitant conditions, n (%)	201 (100)
Cardiovascular disease	142 (70.6)
Renal disease	16 (8)
Hepatic disease	65 (32.3)

previous mean dose of immediate-release metformin (1380 ± 432 mg).

Adherence (primary endpoint) and patient preferences

Almost all patients (96.5%) demonstrated "excellent" adherence to metformin XR (Table 4). The remaining seven patients (3.5%) demonstrated "good adherence". No patient demonstrated < 75% adherence to metformin XR.

Almost all patients (194/201; 96.5%) expressed a preference for metformin XR over immediate-release metformin (Table 4). Six patients (3.0%) preferred immediate-release metformin and one patient (0.5%) did not have a preference. Convenience of use was the main driver of preference and was cited by 88.6% as the primary reason for their choice. Reasons related to tolerability were cited by 3% of the population and reasons relating to efficacy/glycaemic control were cited by 7%.

Table 3: History of type 2 diabetes.

Diabetes duration (y)	
N (%)	201 (100)
Missing (%)	0
Mean (SD)	3.1 (3.3)
Median	1.78
Q1; Q3	1.02; 4.38
Range	0.23-24.2
Duration of IR metformin treatment (months)	
N (%)	201 (100)
Missing (%)	0
Mean (SD)	24.4 (27.9)
Median	12.0
Q1; Q3	6.0; 36.0
Range	2-180
Mean daily dose of immediate release metformin pre-study mg (SD)	
N (%)	201 (100)
Missing (%)	0
Mean (SD)	1380 (432)
Median	1500
Q1; Q3	1000; 1700
Range	250-2000
BID dosing n (%)	196 (97.5)
TID dosing n (%)	5 (2.5)
Duration of metformin XR treatment at baseline (weeks)	
N (%)	201 (100)
Missing (%)	0
Mean (SD)	21.3 (17.5)
Median	14.3
Q1; Q3	8.4; 30.4
Range	4-113.9
Current dose of metformin XR (mg)	
N (%)	201 (100)
Missing (%)	0
Mean (SD)	1275 (447)
Median	1500
Q1; Q3	1000; 1500
Range	500-2250

Table 4: Adherence and patient preference.

N (%)	201 (100)
Missing (%)	0
Excellent (< 90%)	194 (96.5)
Good (> 75-90%)	7 (3.5)
Moderate (> 50-75%)	0
Bad (< 50%)	0
Excellent + good (> 75%)	201 (100)
Metformin XR preferred	194 (96.5)
Metformin IR preferred	6 (3)
No preference	1 (0.5)

Efficacy and tolerability

Measurements of FBG were available for 181 patients at baseline and for 173 patients at 6 months. The dose of metformin XR was changed in only 25 patients

Table 5: Glycemic parameters and vital signs.

	Baseline	After 6 months
FBG		
N (%)	201 (100)	201 (100)
Within normal range of local lab values n (%)	53 (26.4)	87 (43.3)
Below normal range of local lab values n (%)	13 (6.5)	1 (0.5)
Above normal range of local lab values n (%)	115 (57.2)	85 (42.3)
Not assessed	20 (9.9)	28 (13.9)
HbA1c		
N (%)	201 (100)	201 (100)
Within normal range of local lab values n (%)	42 (20.9)	43 (21.4)
Below normal range of local lab values n (%)	12 (5.9)	0
Above normal range of local lab values n (%)	96 (47.8)	86 (42.8)
Not assessed	51 (25.4)	72 (35.8)
Heart rate (beats/min)		
N (%)	201 (100)	199 (99)
Not assessed	0	2 (1)
Mean	73.2 (7.6)	73 (6.2)
Median	72	73
Q1; Q3	68; 78	69; 76
Range	56-105	54-91
SBP (mmHg)		
N (%)	201 (100)	199 (99)
Not assessed	0	2 (1)
Mean	132.3 (10.9)	128.9 (9.8)
Median	131	130
Q1; Q3	125; 140	123; 135
Range	110-160	100-160
DBP (mmHg)		
N (%)	201 (100)	199 (99)
Not assessed	0	2 (1)
Mean	80.4 (7.8)	79.3 (7.5)
Median	80	80
Q1; Q3	75; 85	75; 84
Range	60-100	40-100

(7.5%) during the study. Most of these changes involved an increase in dosage (22 occasions), as opposed to a decrease in dosage (3 occasions).

FBG was above normal (according to local laboratory reference ranges) in 57% of patients at baseline and 42% at study end; corresponding percentages for HbA1c were 48% and 43%, respectively (Table 5). Six percent of patients had FBG and HbA1c below normal at baseline (13 and 12 patients, respectively); at study end, a single patient (0.5%) had abnormally low FBG and no patient had abnormally low HbA1c.

The change in mean heart rate (73.2 ± 7.58 beats/min to 73.0 ± 6.24 beats/min) and diastolic blood pressure (80.4 ± 7.76 mmHg to 79.3 ± 7.54 mmHg) was negligible. A trend towards reduction in mean systolic blood pressure was observed from Visit 1 (132.3 ± 10.93 mmHg) to Visit 5 (128.9 ± 9.75 mmHg).

Twenty-five subjects (12%) reported at least one treatment-emergent AE, among whom four subjects (2%) had reported at least one treatment-related AE (Table 6). Gastrointestinal side-effects occurred in four patients (diarrhoea, dysgeusia, flatulence, irritable bowel syndrome, large intestine polyp). AE associated with any other individual MedDRA classification occurred in one or two patients, except for vascular AE (four with hypertensive crisis, four with hypertension, one with transient ischaemic attack). There was one case of hypoglycaemia. Four AEs or ADRs were considered by investigators to be related to study treatment (one case each of diar-

Table 6: Treatment related Adverse Events (AE).

N (%)	201 (100)
Missing	0
Subjects with at least one treatment related AE, n (%)	4 (2)
Cardiac disorders	
Myocardial ischemia n (%)	1 (0.5)
Gastrointestinal disorders	
Diarrhoea, n (%)	1 (0.5)
Dysgeusia, n (%)	1 (0.5)
Flatulence, n (%)	1 (0.5)
Metabolism and nutrition disorders	
Hypoglycaemia, n (%)	1 (0.5)
Vascular disorders	
Hypertension, n(%)	1 (0.5)
Subjects with at least one treatment related SAE, n (%)	1 (0.5)

rhoea, dysgeusia, flatulence and hypertension). Three patients reported one or more serious AE (myocardial ischaemia, irritable bowel syndrome, hypertension and transient ischaemic attack, the last two occurring in the same patient and considered by the Investigator to be related to treatment).

Discussion

This study showed that adherence to metformin XR, given as initial pharmacologic antidiabetic therapy to 201 type 2 diabetes patients in line with international management guidelines, was "excellent (> 90%) in 96.5% and > 75% in the remaining 3.5%. The overwhelming majority of the patients preferred the once-daily metformin formulation to their previous immediate-release formulation, with about nine patients in ten citing the convenience of their antidiabetic regimen as the principal reason for their choice. There was no signal for a decline in glycaemic control during the six-month observation period, with a trend to improvement, indicating improved glycaemic control despite majority of subjects continuing to receive the same dosage throughout the study. This improvement in glycaemic control could be a reflection of the excellent adherence to therapy. Also, the systolic blood pressure was decreased under the once-daily regimen. The effect of metformin on blood pressure values is currently being assessed in larger clinical trials, e.g. in China.

The preference for metformin XR compared with immediate-release metformin observed in our study has been described previously in other studies. For example, in one study average adherence increased from 62% to 81% in a cohort of 40 patients switched from immediate-release metformin to metformin XR ($p < 0.0001$) [7]. The same study showed that adherence to metformin XR was higher compared with immediate-release metformin in parallel patient cohorts (80% vs. 72%, $p = 0.0026$) [7].

The high level of observed adherence, together with the strong preference for the once-daily regimen, in out study (also consistent with previous clinical experience) [8] are consistent with prior experience that pharmacologic regimens of lower complexity support better adherence than more complex regimens. One study showed that people with type 2 diabetes were nine times more likely to be non-adherent to their antidiabetic regimen if it involved more than one medication intake each day [9]. These observations have clinical importance, as establishing a high level of adherence to antidiabetic therapy is an important determinant of achieving good glycaemic control in type 2 diabetes [10-12]. A low level of adherence has been identified as a predictor of future clinical inertia, where there is a failure to intensify the regimen in future as the quality of glycaemic control declines as β-cell dysfunction progresses [13]. Lower adherence increases the overall cost of treatment for diabetes, when an increased risk of adverse outcomes associated with sub-optimal adherence is taken into account [14]. This is of particular importance for health care systems taking into account the high and increasing prevalence of diabetes. Finally, low adherence predicted an increased risk of adverse clinical outcomes, in people with diabetes, including hospitalization or mortality [15], or complications of diabetes [16]. Importantly, this study employed tablet counting, rather than patients' self-report of adherence, which has been shown to be less reliable than formal observation of adherence in patients with diabetes [17].

Previous studies have explored the effects of a switch from immediate-release to extended-release metformin. Randomised, controlled trials people with type 2 diabetes have shown that switching from twice-daily immediate-release metformin to metformin XR did not result in any diminution of glycaemic control [18,19]. An observational study in 35 patients also showed that switching from immediate-release to extended-release metformin did not compromise metabolic control (glycaemia or lipids) [8], Another observational study suggested improved glycaemic control with this treatment switch, however, that was apparently associated with improved adherence [7]. Finally, a randomised trial suggested improved glycaemic control (mean HbA1c 6.8% vs. 7.3%, $p < 0.05$), along with a reduction in LDL-cholesterol, and improvement in some inflammatory cytokines, in patients randomised to metformin XR vs. immediate release metformin [20]. Overall, these studies are comparable without finding of no reduction (and a trend to improvement) in glycaemic control in patients receiving extended-release metformin in our study.

The European labelling for metformin supports a switch from the immediate-release formulation at the same dose, consistent with the observations of no loss of glycaemic control after the switch, described above. Metformin XR may also be started as the initial metformin preparation for a patient naïve to metformin, however.

Most patients experience gastrointestinal side-effects when initiating metformin; guidance from the UK National Institute for Health and Care Excellence notes that a switch from immediate-release to metformin XR may offer improved tolerability where these side-effects are especially troublesome [3]. A report of four observational studies showed that most patients with gastrointestinal intolerance to immediate-release metformin could be switched successfully to the same metformin XR formulation as used in the present study [21]. Similarly, a retrospective chart review in 205 patients switched from immediate-release metformin to metformin XR showed that after the switch, the frequency of any gastrointestinal adverse event was reduced from 26.34% to 11.71% ($p = 0.0006$) and the frequency of diarrhoea was reduced from 18.05% to 8.29% ($p = 0.0084$) [22].

Only 3% of our population cited issues relating to tolerability as a reason for preferring the extended-release formulation, however. Our patients had previously received immediate-release formulation for at least 8 weeks and were therefore likely to represent a population already demonstrated to be tolerant of metformin, although the reason for the earlier switch between formulations is unknown.

The value of real world data has been recognised increasingly in recent years [23]. In particular, the lack of restrictive enrolment criteria for such studies ensures that patient populations reflect the patients that physicians see in the general practice setting compared with those in the highly structured environment of a randomised, controlled trial [23]. Limitations of the study include its observational, non-interventional design and lack of formal statistical evaluation of glycaemic outcomes.

Conclusions

Adherence to treatment was > 90% in the vast majority of 201 type 2 diabetes patients switched from immediate-release metformin to metformin XR, with no patient demonstrating < 75% compliance. Glycaemic control was maintained or improved. The patients demonstrated a strong preference for metformin XR, compared with their earlier immediate-release metformin regimen, with this choice driven by greater convenience of treatment.

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Ethics

The protocol complied with recommendations of the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments and was conducted in compliance with International Council for Harmonization of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use-Good Clinical Practice (ICH-GCP E6, 1996), consistent with the ethical principles that have their origin in the Declaration of Helsinki. All patients provided signed, informed consent before enrolment.

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