Routine Evaluation Conducted on Registered Drugs (RECORD) – Experience of Glimepiride Oral Tablet in Treatment of Patients with Type 2 Diabetes Mellitus

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Abstract: **Objective** Patients were observed for improvement of diabetic symptoms and/or laboratory parameters in the form of improved RBS, FBS, 2 hr postprandial (PP) reduction rate in blood sugar, HbA1c reduction rate, or improvement in lipid profile. Patients were also assessed for the level of diabetes education they had received. **Methods** Three visits were scheduled for each patient, Baseline visit (visit 1), visit 2 (at 3 months from baseline), and visit 3 (at 6 months from baseline), during which observational data were collected; including patients demographics, diabetes/anti-diabetics history, symptoms & signs of diabetes, diabetes education, concomitant diseases, vital signs, HbA1c, FBG, 2 hr- postprandial & RBG values, lipid profile & creatinine (baseline visit). Changes to anti-diabetic therapy, HbA1c, FBG, 2 hr-postprandial & RBG values were evaluated at 3 & 6 months (visit 2 & 3). Lipid profile and creatinine were evaluated at 6 months. **Results:** The RECORD study demonstrated a statistically significant reduction in the baseline mean RBS level (from 275±86 to 162±43 mg/dl), FBS level (201±60 to 128±32 mg/dl), 2-hr postprandial blood glucose level (282±80 to 172±46 mg/dl) and HbA1c percentage (9.4±2 to 7.4±1.5 %) at the study endpoint (6 months duration), p value < 0.001 after a mean glimepiride daily dose of 2.36 ± 1.04 mg. Diabetic symptoms, especially; polyuria, polyphagia, polydipsia, numbness/tingling, burning sensation, and visual disorders showed significant improvements throughout the study duration. Glimepiride was well tolerated by the study population, and adverse events (AEs) were reported in 22 (1.35%) patients. All AEs were mild to moderate in intensity, none were serious and all AEs recovered without any sequelae. AEs included headache (8 patients), nausea (5 patients), dizziness (4 patients), diarrhea (3 patients) and hypoglycemia (2 patients). There was no causal relationship of the AEs to the study medication except in 2 patients who experienced hypoglycemia (one graded as mild and the other as moderate). **Conclusion** Glimepiride therapy in type 2 diabetic patients, showed safe and significant reduction in blood glucose parameters including HbA1c values, with significant improvements in diabetes symptoms over 6 month duration; demonstrating high effectiveness and tolerability among study population.

[Ayda Wassfy. **Routine Evaluation Conducted on Registered Drugs (RECORD) – Experience of Glimepiride Oral Tablet in Treatment of Patients with Type 2 Diabetes Mellitus.** *Life Sci J* 2012;9(4):2127-2134] (ISSN: 1097-8135). http://www.lifesciencesite.com. 317

Keywords: Routine Evaluation; Registered Drugs; Glimepiride Oral Tablet; Patient; Type 2 Diabetes Mellitus

Abbreviation

ADA	American Diabetes Association	BMI	Body Mass Index	CAD	Coronary Artery Disease
FBS	Fasting Blood Sugar	GIT	Gastrointestinal Tract	HbA1c	Glycated Hemoglobin
HDL	High Density Lipoprotein	LDL	Low Density Lipoprotein	LPO	Last Patient Out
OAD	Oral Anti-Diabetic(s)	RBS	Random Blood Sugar		
SmPC	Summary of Product Characteristics	SU	Sulfonylurea(s)	T2D	Type 2 Diabetes

1. Introduction

Type 2 diabetes (T2D) is a progressive disorder with a consistent and steady increase in glycosylated hemoglobin (HbA1c) over time, associated with enhanced risk of micro- and macrovascular complications and a substantial reduction in life expectancy.[1]

It is a chronic disease associated with insulin resistance and a progressive failure of the pancreatic beta cells.[2-4] T2D is believed to account for about 90% of all cases of diabetes.[5] The American Diabetes Association (ADA) reported that, in the USA in 2007, 17.5 million people were diagnosed with diabetes.[6]

The 2010 International Diabetes Federation IDF atlas, indicates that the total number of diagnosed cases of diabetes (20-79 years age group) in 2010 is 17.96 (6.6%) millions in south America and Canada, 37.36 (10.2%) millions in north America and Caribbean region, 76.71 (4.7%) millions in Western Pacific region, 58.67 (7.6%) millions in South-East Asian region, 12.09 (3.8%) in Africa, and 26.65 (9.3%) in Middle East and North Africa; totaling to a global prevalence of 284.81 (6.4%) millions. According to the IDF 2010 atlas, there are 4.79 (11.4%) million case diagnosed with diabetes in Egypt, and the number is increasing at a rate of 8 new cases in every

100,000 person per year, with a mean yearly health expenditure of 0.55 billion USD (116 USD/person with diabetes) — all IDF percentages are for comparative prevalence adjusted to the world population.[7]

The number of people with diagnosed diabetes is growing at a rate of 1 million per year[8], and is projected to reach over 48 million by 2050. [9] The impact of diabetes on the US economy is alarming, with a total estimated cost of US$174 billion in 2007. A majority of these costs are for treatment of complications of the disease.[10-13]

Large population-based studies have established that diabetes is associated with increased rates of cardiovascular morbidity and death. Clinical trials have shown the benefits of intensive glucose lowering therapies to reduce the risk of microvascular disease, cardiovascular events and death, or the combined risk of micro- and macrovascular events, in diabetic patients. Diabetes-related complications greatly diminish patients' health-related quality of life.[14]

The combination of dietary measures, body weight control and physical exercise is known to promote glycaemic control in patients with T2D. In 40% to 60% of these patients, however, this combination appears to be insufficient to achieve adequate blood glucose control and, in such cases, administration of one or several oral anti-diabetic drugs (OADs) is then added on to the initial measure.[15]

The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) published an expert consensus statement on the approach to management of hyperglycemia in individuals with type 2 diabetes. Highlights of this approach are: intervention at the time of diagnosis with metformin in combination with lifestyle changes (MNT and exercise) and continuing timely augmentation of therapy with additional agents (including early initiation of insulin therapy) as a means of achieving and maintaining recommended levels of glycemic control (i.e., A1C <7% for most patients). As A1C targets are not achieved, treatment intensification is based on the addition of another agent from a different class. The overall objective is to achieve and maintain glycemic control and to change interventions when therapeutic goals are not being met.[16]

Most clinical evidence shows that the glucose-lowering effect of sulfonylureas and metformin is not durable and that the loss of glycemic control is associated with progressive β-cell failure. Metformin is traditionally known for its metabolic effects on the liver; and other metformin target tissues include skeletal muscle and adipose tissue. Metformin is a useful adjuvant to lifestyle modification in overweight and obese patients with type 2 diabetes mellitus, metabolic syndrome, or impaired glucose tolerance (IGT).[17]

Sulfonylureas, which have been used for many years to treat T2D, decrease blood glucose by stimulating insulin secretion from pancreatic ß cells. The extra-pancreatic actions of these drugs also contribute to their hypoglycemic action.[18]

Major complications associated with SU agents are hypoglycemia, weight gain and the exhaustion of beta (ß) cells with its hyperinsulinemic effect. Insulin resistance ultimately involves the development of obesity, metabolic disorder, hypertension and atherosclerotic diseases.[19]

Glimepiride is a long-acting SU of recent origin. The glucose-lowering effects are well documented and comparable with those of other long-acting SUs.[1]

In comparison with conventional sulfonylurea drugs, glimepiride has several benefits: rapid and complete absorption after oral administration, a lower dose, long duration of action, and possible insulin-sensitizing effect. In addition, previous clinical studies demonstrated that glimepiride once-daily dose, which is a common usage of this agent in Europe and the US, provided a good glycemic control of T2D as well as twice-daily doses. [20]

As monotherapy, glimepiride is well tolerated and effective in achieving metabolic control in treatment of patients with T2D. [1]

Although glimepiride has lesser insulin secretion action from the pancreatic β-cells compared with the conventional SU agent, its hypoglycemic action is equivalent to conventional SU agents.[19] It has recently been reported that plasma adiponectin levels increase after the administration of glimepiride[21]. Adiponectin shows anti-atherosclerotic effects on the vascular wall, and insulin sensitivity is increased in skeletal muscle and liver. The unique effects of this drug might be useful in patients with metabolic syndrome.[19]

There are clinical trial outcomes suggesting that glimepiride contributes to the improvement of hyperinsulinemia, visceral fat accumulation and atherosclerotic suppression, and that glimepiride was found to improve insulin resistance, consistent with results reported in previous studies.[19]

Without markedly increasing plasma insulin concentrations, glimepiride has a more prolonged hypoglycemic effect than glibenclamide, suggesting that glimepiride might have more

potent extra-pancreatic action.[18]

Glimepiride differs from other sulfonylureas in that it reportedly binds to a different receptor at the ß-cell membrane than other agents in this class. Animal studies demonstrate greater reductions in plasma glucose per increment in plasma insulin with glimepiride than with glibenclamide or glipizide, suggesting that glimepiride may have direct extra pancreatic effects that stimulate an improvement in insulin sensitivity.[22]

Glimepiride is characterized by a long duration of action, conferring effective glycaemic control over a 24-hour period with a single daily dose. The efficacy and good safety profile of glimepiride in patients with type 2 diabetes have been clearly demonstrated in previous studies employing doses ranging from 1 mg to 6 mg/day.[15]

Some clinical researchers have also reported that neither weight nor BMI is increased after the administration of glimepiride.[23-24] In a recent study, in agreement with these reports, results have shown no significant change in BMI.[19]

An intervention targeting reduction in glycaemia levels to current guidelines, as well as improving concomitant risk factors, such as blood pressure, lipid levels and bodyweight might prevent and reduce the risk of micro- and macro-vascular complications. This intervention has recently been endorsed by a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association.25

Improvements in the cardiovascular event rates are important as these events are the main contributor to death and increased cost of treating T2D.[14]

Recent drug strategies are also targeted to improve insulin resistance rather than the promotion of insulin secretion.[19]

Glimepiride leads to an improvement in lipid metabolism [26], improves endothelial function due to the biosynthesis of nitric monoxide, and has anti-oxidative effects in addition to the anti-atherosclerotic effects mediated by cytokines. [27,28] Furthermore, glimepiride also has an inhibitory effect on the initiation and development of atherosclerosis.[19]

This study observed the effectiveness and safety of Glimepiride treatment in type 2 diabetes mellitus, and assessed how challenging it can be to achieve targeted treatment outcomes, safely and effectively within a practical clinical setting.

2. Patients and Methods

Patients

Two thousand patients were planned for enrollment. Physicians were guided by the SmPC (Summary Of Product Characteristics) in deciding on the treatment regimen and patient selection. All patients presenting with type 2 diabetes mellitus (T2D) for whom the physician decided to prescribe Glimepiride were enrolled in the study.

Study Design

The RECORD study was designed as a national, multicentre, prospective, observational study, and was conducted in Egypt over 4 years duration The study duration for any one patient was 6 months, starting from the recruitment day (individual baseline), till visit 3 (6 months from individual baseline).

Observations

Three visits were scheduled for each patient, baseline visit (visit 1), visit 2 (at 3 months from baseline), and visit 3 (at 6 months from baseline), during which observational data were collected; including patients demographics, diabetes/anti-diabetics history, symptoms & signs of diabetes, diabetes education, concomitant diseases, vital signs, HbA1c (glycosylated hemoglobin), FBG (Fasting Blood Sugar), 2 hr-postprandial & RBG (Random Blood Sugar) values, lipid profile & creatinine (baseline visit). Changes to anti-diabetic therapy, HbA1c, FBG, 2 hr-postprandial & RBG values were evaluated at 3 & 6 months (visit 2 & 3). Lipid profile and creatinine were evaluated at 6 months. Adverse events were monitored throughout the course of the study. The usual initial dose was 1 mg once daily, and was allowed to be gradually up titrated (1mg - 2 mg- 3 mg - 4 mg - 6 mg), as required based on regular monitoring of blood glucose levels.

Efficacy Outcome

Patients were observed for improvement of diabetic symptoms and/or laboratory parameters in the form of improved RBS, FBS, 2 hr postprandial reduction rate in blood sugar, HbA1c reduction rate, or improvement in lipid profile. Patients were also assessed for the level of diabetes education they had received.

Safety Outcome

Patients were observed for the occurrence of any adverse events, including causal relationship to study medication, measures taken, and outcome.

Statistical Analysis

Descriptive methods were used for the analysis of the study outcomes, including calculation of appropriate measures of the empirical distribution

(mean, standard deviation, median, minimum, maximum, for continuous variables, and frequencies & percentages for categorical variables) as well as calculation of descriptive p-values for group comparisons. Quantitative data were analyzed for normal distribution using paired t-test and repeated measures analysis. Qualitative data were analyzed using Chi square test.

3. Results

Patients' Baseline Characteristics and Demographics

A total number of 1629 patients with T2D mellitus were enrolled in the study. The study population had a balanced contribution from both male and female patients (49.8%, n=811 males and 50.2%, n=818 females) with a mean age of 55.23 ± 10.49 (years), a mean weight of 85.74 ±15.16 (kg), a mean height of 1.67 ± 0.08 (m), a mean BMI of 30.86 ± 5.9 (kg/m^2), and a mean duration of diabetes of 10.36 ± 5.83 (years).

The mean baseline random, fasting and 2 hours postprandial blood glucose levels (mg/dl) levels were 275.3 ± 86.4, 200.7 ± 60.2 and 282.3 ± 80.4 respectively. The mean HbA1c level was 9.4 ±2.0.

The most frequently reported diabetic symptoms among the study population at visit 1were polyuria, polyphagia, polydipsia and numbness constituting 89.2% (n=1453), 75.3% (n=1226), 77.5% (n=1262) and 57.9% (n=943) respectively, and less frequently burning sensation 50.7% (n=826) and visual disorders 31.1% (n=507).

The highest rate of concomitant diseases among the study population was for hypertension (45.2%, n=737), hepatic disorders (12.5%, n=204) GIT (Gastro-Intestinal Tract) disorders (11.4%, n=185). Cardiovascular and renal diseases were less frequently recorded at 9.9% (n=162) and 7.7% (n=125) respectively.

Analysis of data concerning diabetes education received by patients revealed that 56.6% (n=922) of patients had been previously educated on disease background, 68.1% (n=1110) had been educated on diet, 55.9% (n=910) on exercise, 44.9% (n=731) on foot care, 35.6% (n=580) on eye care and 30.4% (n=496) on diabetic complications.

The mean glimepiride daily dose prescribed at baseline was 2.36 ± 1.043 mg where the most frequent dosage forms were **3 mg** (25.4%) then **2 mg** (21.5%) while the most frequent concomitant OADs were metformin (18.4%), gliclazide (12.9%) and amophage by 8.9%.

Outcomes

The RECORD study demonstrated a significant reduction in the baseline mean RBS (from 275.3± 86.4 to 187.4 ± 57.3 at visit 2 (3 months from baseline) to 162.3 ± 42.9 mg/dl with mean percent reduction 41% at visit 3 (end of study), p <0.001).

Baseline mean fasting blood glucose levels also showed a significant reduction (from 200.7 ± 60.2 to 145.5 ± 42.7 at visit 2 to 128.4 ± 31.9 mg/dl with mean percent reduction of 36% at visit 3, p<0.001), with similar statistically significant reduction in the mean baseline 2-hr postprandial blood glucose levels (from 282.3 ± 80.4 to 202.0 ± 59.7 at visit 2 to 171.7 ± 46.2 mg/dl with mean percent reduction of 39.2 % at visit 3, p <0.001).

The mean value of HbA1c percentage showed statistically significant reduction from 9.4 ± 2.0 at baseline 8.0 ± 1.6 at visit 2 to 7.4 ± 1.5 and mean percent reduction of 21.3% at visit 3 (p<0.001).

Diabetic symptoms, especially; polyuria, polyphagia, polydipsia, numbness/tingling, burning sensation, and visual disorders showed statistically significant improvements with time through visit 2 (3 months) and visit 3 (6 months) as outlined in Table 2 below.

Both mean systolic (SBP) and diastolic blood pressure (DBP) values at baseline (SBP =139.7 ± 20.3 mmHg, DBP = 86.9± 10.4 mmHg), showed significant gradual reduction, to reach 130.98 ± 13.92 mmHg, and 82.1 ± 7.0 mmHg, for SBP and DBP respectively by end of study; at visit 3. (p <0.001), representing a reduction of 8.72, and 4.77 mmHg, in SBP and DBP, respectively, compared to baseline values.

In the other hand, the BMI (Body Mass Index) was significantly decreased from 30.86± 5.89 kg/m^2 at visit 1 to 30.65 ± 5.59 kg/m^2 at visit 3 (p <0.05).

Concerning the lipid profile values, there were statistically insignificant reduction in the mean values of LDL (Low Density Lipoprotein) from 148.8 ± 42.9 at visit 1 to 146.1 ± 42.8 at visit 3 (p =0.183), for triglycerides there were statistically significant reduction from 209.8 ± 79.9 at visit 1 to 190.1 ± 63.5 at visit 3 (p <0.001), and for cholesterol from 228.9 ± 44.3 at visit 1 to 221.9 ± 36.6 at visit 3 (p <0.001). While the mean value of HDL (High Density Lipoprotein) showed an insignificant slight increase from 47.5 ± 26.6 at visit 1 to 47.7 ± 23.8 at visit 3 (p = 0.802). Regarding the level of serum creatinine (mg/dl), the results revealed a very trivial decline in the mean value from 1.1 ± 0.3 at visit 1 to 1.0 ± 0.3 at visit 3 (p <0.001).

Safety Profile

Glimepiride was well tolerated by the study population, with 22 patients (1.35%) showing adverse events of mild to moderate intensity, mainly in the form of headache, nausea, dizziness, diarrhea and hypoglycemia (2 patients), all recovered with no sequelae. Both hypoglycemic events were of mild to moderate intensity and recovered with no sequelae, and one patient with hypoglycemic event required dose reduction. There was no causal relationship of AEs (Adverse Events) to the study medication except in 2 patients who experienced hypoglycemia. There have been no serious adverse events recorded.(all adverse events were defined according to International Conference for Harmonization-Good Clinical Practice guidelines—ICH-GCP).

Table (1) The mean values of Lab. results (*Random Blood Sugar* (mg/dl), *Fasting Blood Sugar* (mg/dl), *2 hrs-postprandial Blood Sugar* (mg/dl) and *HbA1c %*) at different study visits.

Laboratory Test	Visit	Mean Value (SD)	% Mean Change	P Value*	P Value**
Random Blood Sugar level mg/dl	Visit 1 Baseline	275.3 (86.4)	NA	NA	<0.001
	Visit 2 3 Months	187.4 (57.3)	31.9	<0.001	
	Visit 3 6 Months	162.3 (42.9)	41	<0.001	
Fasting Blood Sugar level mg/dl	Visit 1 Baseline	200.7 (60.2)	NA	NA	<0.001
	Visit 2 3 Months	145.5 (42.7)	27.5	<0.001	
	Visit 3 6 Months	128.4 (31.9)	36	<0.001	
2 hrs-postprandial Blood Sugar level mg/dl	Visit 1 Baseline	282.3 (80.4)	NA	NA	<0.001
	Visit 2 3 Months	202.0 (59.7)	28.4	<0.001	
	Visit 3 6 Months	171.7 (46.2)	39.2	<0.001	
HbA1c %	Visit 1 Baseline	9.4 (2.0)	NA	NA	<0.001
	Visit 2 3 Months	8.0 (1.6)	14.9	<0.001	
	Visit 3 6 Months	7.4 (1.5)	21.3	<0.001	

* Using paired t-test

** Using repeated measure analysis

Table 2: Diabetes History of symptoms at visit 1 and sequelae of symptoms at visits 2 and 3

	Visit 1		Visit 2			Visit 3		
	Freq.	%	Improved %	No change %	Worsened %	Improved %	No change %	Worsened %
Polyuria	1453	89.2	86.6%	10.2%	3.2%	90.1%	6.9%	3.0%
Polyphagia	1226	75.3	85.5%	10.3%	4.2%	90.0%	6.8%	3.2%
Polydipsia	1262	77.5	86.0%	12.0%	2.0%	89.7%	7.3%	3.0%
Numbness/Tingling	943	57.9	83.4%	11.9%	4.7	85.7	12.4	1.9
Burning sensation	826	50.7	68.2%	26.0	5.8%	83.6	13.6	2.8
Visual disorders	507	31.1	71.2%	23.7%	5.1%	82.0	15.3	2.7

Table 3: Adverse events characteristics

Adverse events characteristics	**Frequency**		
Adverse events	22 (1.35%)		
Seriousness	Yes	0	
	No	22	
		Mild	Moderate
	Headache	3	5
	Hypoglycemia	1	1
	Nausea	3	2
	Dizziness	1	3
	Diarrhea	2	1
Intensity	Moderate	12	
	Mild	10	
Causal relationship	Yes	2*	
	No	20	
Remedial Measures	Dosage decreased	5	
	No change	17	
Outcome	Recovery without sequel	17	
	No change	22	

* Two patients suffered hypoglycemia related to Amaryl® administration

3. Discussion

The study population demonstrated a clinical setting very similar to what is encountered in practice. The majority of the patients had been diabetics for long (mean duration 10.36 years), having a combination of concomitant diseases, notably hypertension (45.2%), hepatic disease (12.5%), or cardiovascular disease (9.9%). The majority of the patients received education about their disease, however, in most cases information was lacking; especially regarding eye care and diabetic complications, where two thirds of the patients were never educated in these two particularly important topics. Glimepiride, demonstrated significant improvements in all diabetic symptoms after visit 2 (3 months), and improvements continued further as recorded in visit 3 (6 months).

All diabetic parameters (RBS, FBS, 2hrs pp levels, HBA1c) showed marked improvement, with good control of the disease, and excellent tolerability. No serious adverse events were recorded, and side effects were either mild or moderate, and recovered with no sequelae.

In a retrospective cohort study conducted using an academic health center enterprise-wide electronic health record (HER) system to identify 11,141 patients with T2DM with or without a history of previous CAD (Coronary Artery Disease), treated with either glipizide, glibenclamide, or Glimepiride. Patients were followed for mortality rates. Subanalysis of patients with documented CAD, showed a strong trend toward a reduced risk with Glimepiride, and suggested that glimepiride may be the preferred sulfonylurea in those with underlying CAD. [29] In this study, both systolic and diastolic blood pressure values showed significant improvement by end of study, together with similar improvements in lipid profile with a cardiovascular protective attitude (increased HDL, and decreased LDL, cholesterol, and triglycerides). Creatinine was also reduced from 1.1mg/dl at baseline to 1.0 mg/dl on visit 3 (end of study), indicating an improvement in renal functions. Tsunekawa et al.[30] clearly demonstrated that glimepiride actually increases insulin sensitivity in type 2 diabetic patients. They also proposed that the increase in insulin sensitivity might be associated with increased adiponectinemia. the improvement in glycemic control, insulinemia, and adiponectinemia by glimepiride is of potential benefit to decrease risk factors of atherosclerosis in type 2 diabetic patients. The mechanisms of the increased adiponectinemia by glimepiride may be complex and multifactorial.[31]

In this study Glimepiride has shown to be a safe and effective oral anti-diabetic agent, with good control of symptoms, and provided additional improvements to other organ systems, especially cardiovascular and renal functions.

In addition to safety and efficacy of glimepiride in T2D, it is worth mentioning that glimepiride's ease of use provides an affordable solution to "medicated compliance", which is a common problem among diabetic patients. Once-daily dose compared with more frequent dosing regimen promises to improve compliance among patients with NIDDM (Non-Insulin Dependent Diabetes Mellitus) [19]. In addition, glimepiride is available in different preparation concentrations (1,2,3,4, and 6 mg), which further adds to its ease of use. A recent randomized crossover study has shown that pharmacodynamic and safety profiles in once-daily dose of glimepiride in type 2 diabetic patients are not different from those in twice-daily dosing, and suggested that once-daily dosing is more suitable for the type 2 diabetic patients treated with glimepiride [19].

Further patient education is recommended in order to maximize the individual benefits, and minimize the potential risk imposed on disease ignorant or misinformed patients.

Conclusion

This study showed that glimepiride was

effective as an antidiabetic therapy for type 2 diabetic patients, who were able to achieve target metabolic control in terms of reduction of blood glucose parameters, including HbA1c values. Moreover, glimepiride therapy improved diabetic symptoms, and all reported AEs (1.35%) were of mild to moderate intensity, indicating high tolerance to glimepiride therapy.

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10/10/2012