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SAFETY AND EFFICACY OF REMOGLIFLOZIN ETABONATE IN PATIENTS WITH INADEQUATELY CONTROLLED TYPE-II DIABETES MELLITUS

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ABSTRACT

The objective of present study is to evaluate the safety and efficacy of Remogliflozin Etabonate in uncontrolled Type-II Diabetes Mellitus patients along with Metformin during different treatment periods and comparison with Metformin and Teneligliptin therapy. Methods: The effect of therapy on glycemic maintenance and other biological parameters in 353 patients were assessed using appropriate statistical analysis. Results: Occurrence of hypoglycemic attacks was nil and hypotensive incidents were very minimal during Metformin and Remogliflozin($M+R_{1,2}$) therapy compared to Metformin and Teneligliptin(M+T). Other biochemical parameters related to Diabetes Mellitus also had significant declination from their initial values after ($M+R_{1,2}$) than that of (M+T) therapy.

Keywords: Remogliflozin Etabonate, Type-II Diabetes Mellitus, Teneligliptin, Metformin, Sodium glucose co-transporter 2(SGLT-2)

INTRODUCTION

Diabetes is a group of metabolic disorder characterised by hyperglycaemia [1]. It was broadly classified into 2 types i.e., Type-I and Type-II Diabetes Mellitus [2]. The later was earlier thought to be component of metabolic syndrome[3] but further identified that it results from interaction between genetic, environment and behavioural risk [4,5]. The biggest challenge now a days for a health care provider is to address the continuous needs and demands of individuals with chronic illness like Diabetes [6]. As per the treatment guidelines of Diabetes Mellitus the recommended first line therapy is Metformin, but when this fails in achieving glycemic control other Oral Hypoglycemic Agents are included as add on therapy with the earlier to obtain better control [7,8]. Kidneys play important role in the maintenance of glucose homeostasis [9]. The reabsorption glucose in renal tubule is mediated by GLUT's and SGLTS's. The later are membrane proteins belonging to the large family and use the electrochemical sodium gradient as energy source produced by Na^+/K^+ adenosine triphosphate [9,10-13]. Remogliflozin Etabonate, a novel, potent, selective sodium glucose transporter 2 inhibitor [14], reduces the glucose reabsorption at kidney increase the glucose excretion and decline plasma glucose levels in Type-II Diabetes patients and also had proven effects in reducing blood glucose levels. Effects of Remogliflozin in combination with Metformin compared with Metformin and Teneligliptin duo for better management.

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MATERIAL AND METHODS

Study design and Subjects: It is a prospective observational comparative study conducted in patients with uncontrolled Type-II Diabetes Mellitus patients in Warangal, Telengana state. The Study Protocol, Data Collection Sheet and Informed Consent Forms were submitted and got approved from the Institutional Human Ethics Committee. A total of 525 patients were screened for the study. Of these 353 patients satisfied the inclusion criteria and were randomised into 3 treatment periods *i.e.*, M+T and $M+R_{(1,2)}$. {$M+R_1$, $M+R_2$- 4 & 8 weeks usage of Remogliflozin Etabonate respectively}.

Measurements: FBS & PLBS were assessed; HbA1c was assessed once in every 2 to 3 months using HPLC method (Boron affinity). Lipid profile (ultracentrifugation with chemical analysis) & serum Creatinine (Jaffe reaction using alkaline picrate) values were assessed in all the three

treatment periods. All the patients included in the study were also assessed for Dizziness, Headache, Myospasm, Abdominal pain, Hypotension, Hypoglycaemia & Genital tract infections.

Statistical analysis: All the parameters were expressed as Mean ± Standard Deviation (SD). Data analysis was performed using MS Excel and Graph pad Prism 8.0 Version. ANOVA (Analysis Of Variance) One Way Method followed by Dunnett's test was performed to assess the significant difference between the Efficacy parameters of Remogliflozin Etabonate and Teneligliptin with Metformin. A p value of <0.0001 was considered to be significant.

RESULTS AND DISCUSSION

353 patients were recruited in this study based on inclusion and exclusion criteria (n=353), gender and age distribution is presented in Table-1. Mean age of study was 52.41±10.21 and majority were in the age group of 51-60. 175 and 178 were Male and Female respectively. Overall, both Teneligliptin and Remogliflozin Etabonate were well tolerated in their respective treatment periods. No severe adverse events were reported in the duration of study. The tolerability profile of M+T & $M+R_{(1,2)}$ (Dizziness, Genital Tract Infections, Myospasms, Headache, Hypotension, Hypoglycaemia & Abdominal pain) were assessed and the values are represented in Table 2 are 5.38%,1.97%, 5.66%,4.53%,0.28%,0% & 1.41% respectively. The results obtained had shown some abnormalities but further evaluation is required to assess whether the drug alone or by itself produced such events in the patients.

Clinical characteristics of patients during all three treatment periods were compared and found to be comparable with respect to demographic and clinical parameters. All the clinical parameters assessed except body weight attained p value of <0.0001**** significance includes (FBS, PLBS, HbA1C, SBP, DBP, S. CREAT, LDL, TG) & Change in body weight was not significant in M+T vs. $M+R_1$, M+T vs. $M+R_2$.

Table 1: Age and Gender distribution in the sample

AGE	**NO. OF PATIENTS**
31-40	45
41-50	115
51-60	119
61-70	60
71-80	14
GENDER	**NO.OF PATIENTS**
Male	175
Female	178

Table 2: Safety and Tolerability profile

Safety parameters	**M+T**	**$M+R_1$**	**$M+R_2$**
Dizziness	30	24	19
Genital tract infections	11	9	7
Myospasms	28	24	20
Headache	28	21	16
Hypotension	3	2	1
Hypoglycaemia	0	0	0
Abdominal pain	10	6	5

Table 3: Clinical parameters comparison of Remogliflozin & Teneligliptin with Metformin

Based on the results obtained it is clear that there is significant decrease in the clinical parameters after 8

Parameters	**Mean values**		**p value**	**Mean values**		**p value**
	M+T	**M+R_1**		**M+T**	**M+R_2**	
FBS	178.49±44.75	135.36±27.12	<0.0001****	178.49±44.75	110.25±12.98	<0.0001****
PLBS	271.40±69.49	196.96±44.49	<0.0001****	271.40±69.49	157.98±22.48	<0.0001****
HbA1C	8.70±1.28	7.85±0.94	<0.0001****	8.70±1.28	7.33±0.68	<0.0001****
SBP	139.90±14.95	129.80±10.81	<0.0001****	139.90±14.95	122.17±7.20	<0.0001****
DBP	85.82±9.06	81.79±61.5	<0.0001****	85.82±9.06	79.35±4.61	<0.0001****
BODY WT	62.86±9.98	62.12±9.78	0.5032	62.86±9.98	61.76±9.77	0.2371
S.CREAT	0.95±0.16	0.89±0.15	<0.0001****	0.95±0.16	0.88±0.15	<0.0001****
LDL	139.94±30.18	116.42±24.04	<0.0001****	139.94±30.18	100.67±16.04	<0.0001****
TG	251.57±111.8	193.55±64.64	<0.0001****	251.57±111.8	167.59±36.17	<0.0001****

weeks usage of Remogliflozin Etabonate than 4 weeks and much significant than Teneligliptin when combined with Metformin i.e., [M+R_2]>[M+R_1]>[M+T].

CONCLUSION

Remogliflozin Etabonate is a newer drug and has a very low potential to interact with other drugs affecting the P450 system. RE had reduced HbA1c levels by an average of 0.5 -- 1.0% after therapy in drug-naive patients with T_2DM. Advantages of RE include modest weight loss of ~ 2 kg, low risk of hypoglycemia, and a trend toward decrease in blood pressure. Safety and Efficacy of RE in patients with T_2DM who had inadequate glycaemic control on Metformin & Teneligliptin. RE led to clinically significant improvements in efficacy parameters in glycaemic control, SBP, DBP, Serum Creatinine, LDL, TG & HbA1c and had no significant effect on Weight Loss. The results concluded that adverse effects reported with RE are low and less severe. However, further studies are needed to establish its long-term safety and efficacy, and to determine whether it has specific advantages over currently approved SGLT2 inhibitors.

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Competing Interests

The Authors declare that they have no competing interests.

Authors Contribution

Anila T. and Priyanka V. may be considered as first authors and worked in the Hospital in collection of data, Counselling the Diabetic patients, etc., Achyuth P. and Venkatesh L. designed the documents required for the work, Dr. B. Siva Subrahmanyam was helpful as Clinical guide in selection of Patients, making them understand about the research work and treatment, E. Venkateshwarlu dragged the results by applying suitable statistical designs, Kottai Muthu A. and Sharavana bhava B.S. discussed and conceived the idea of doing this research work and prepared the Project proposal.

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