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Efficacy and safety of substituting teneligliptin with hydroxychloroquine in inadequately controlled type 2 diabetes subjects with combination therapy of teneligliptin, metformin and glimepiride with or without other antidiabetic therapy: The TENE-HYQ SHIFT Study

ABSTRACT

Introduction. To confirm the efficacy and safety of substituting teneligliptin with hydroxychloroquine in inadequately control type 2 diabetes patients (T2DM) despite treatment with teneligliptin, metformin and glimepiride with or without other antidiabetic therapy.

Material and methods. This is a multicentre observational, retrospective, 24 week clinical study performed in type 2 diabetes patients with HbA_{1c} in the range of 7.5% to 9.5%. This patients were on teneligliptin 20 mg in addition of metformin and glimepiride with or without other antidiabetic therapy. Teneligliptin 20 mg treatment was replaced by hydroxychloroquine 400 mg. The primary endpoint was change in fasting blood glucose (FBG), postprandial blood glucose (PPBG) and HbA_{1c} from baseline to week 24. The secondary outcome of the study was the proportion of patients who achieved good glycaemic control (HbA_{1c} < 7%) and change in estimated glomerular filtration rate (eGFR), blood urea, serum creatinine and lipid profile levels by the end of the study. Data was taken from patients medical records of the Hospital and Private clinic.

Results. Total of 500 patients' data was analysed and after 24 week of follow up these patients presented with significant decrease in HbA_{1c} (–1.1 ± 0.17%; p = 0.000); FBG (–29.87 ± 8.9 mg/dl), PPBG (–56.89 ± 9.2 mg/dl) with 52% of patients had achieved HbA_{1c} levels < 7% at the end of the study which confirmed superiority of switching to hydroxychloroquine from teneligliptin. It has also been observed that after the switch from teneligliptin to hydroxychloroquine there was no change in serum creatinine and eGFR and further statistically significant change in total cholesterol,

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triglycerides and LDL levels with marginal increase in HDL level.

Conclusions. In T2DM patients inadequately controlled on teneligliptin 20 mg along with combination of metformin and glimepiride with or without other antidiabetic therapy, substitute with hydroxychloroquine 400 mg may be a simple yet effective therapeutic option with clinical benefit beyond strict glycemic control without compromising patient's safety. (Clin Diabetol 2018; 7, 5: 209–214)

Key words: hydroxychloroquine, teneligliptin, type 2 diabetes, HbA_{1c}

Introduction

Type 2 diabetes is a progressive disease which is characterized by insulin resistance and diminished insulin secretion [1]. The key management goals of type 2 diabetes mellitus (T2DM) are to achieve target glycemic control ($HbA_{1c} \leq 7\%$) and prevention of long term complications, whilst avoiding hypoglycaemia [2]. As per American Diabetes Association (ADA) 2016 Guidelines [3], lowering A_{1c} below or around 7.0% has been shown to reduce microvascular and macrovascular complications (if implemented soon after diagnosis).

When treatment goals are not achieved with lifestyle modifications and strict dietary regimen, pharmacological treatment is advised. To optimize the management of type 2 DM, several oral antihyperglycemic agents are available.

Towards achieving good glycemic target, a combinations of multiple oral antidiabetic drugs often are required even with and add on insulin among inadequately controlled Indian type 2 diabetes patients. Now a days metformin plus sulfonylurea combination, Dipeptidyl Peptidase-4 (DPP-4) inhibitors is the most suitable agent among non-insulin agents to add-on. Teneligliptin have a structure which is unique and binds to S1, S2, and S2 extensive sub site of DPP-4 enzyme [4]. It is recommended once-a-day administration. Excretion of teneligliptin metabolites is by dual mode [5]. Moreover multiple trails on DPP-4 inhibitors have shown better glycemic control in type 2 diabetes mellitus patients and these patients had minimal risk of hypoglycemia and weight gain [6].

Hydroxychloroquine slows down insulin clearance. This is done possibly by stabilising intracellular lysosomes and slowing the breakdown of internalized insulin-receptor complex and therefore inhibit cystosolic insulin metabolizing enzyme [7]. In 2014 DCGI (Drug Controller General of India) has approved the use of Hydroxychloroquine as an add-on drug to metformin and sulfonylurea in patients with uncontrolled T2DM.

In a RCT trial [8] hydroxychloroquine had demonstrated a potent efficacy of HbA_{1c} reduction as compare to teneligliptin in uncontrolled type 2 diabetes patients who are on metformin and glimepiride combination. Moreover 61% patients who were on hydroxychloroquine based therapy achieved $HbA_{1c} < 7\%$ whereas only 42% patients with teneligliptin based therapy had achieved the same. Even in recently conducted two trials [9, 10], hydroxychloroquine when compared to sitagliptin and vildagliptin shows a statistically significant reduction in HbA_{1c} with similar effect on other glycemic parameters. An abstract presented at AACE (American Association of Clinical Endocrinologists) 2017 by Dr. Shank Joshi [11], confirms the potent ability of hydroxychloroquine to reduce HbA_{1c} in uncontrolled diabetic patients, HbA_{1c} was reduced from 8.9% to 8.1% within 12 weeks.

Based on previous data, it is hypothesized that substituting inadequately controlled T2DM patients from teneligliptin based therapy to hydroxychloroquine based therapy will help to achieve better glycemic control in terms of HbA_{1c}, FBG and PPBG reduction with additional cardio and reno protective benefits being continued with other medications.

The main purpose of the study was to assess the efficacy and safety of substituting teneligliptin with hydroxychloroquine in inadequately controlled type 2 diabetes patients with combination therapy of teneligliptin, metformin and glimepiride with or without other antidiabetic therapy.

Material and methods

The study was carried out at multiple hospitals and private clinic centres of India. This is a multicentre observational, retrospective, 24 week clinical study performed from August 2017 to March 2018. Data was collected from patient's case notes, medication and treatment chart or prescription, laboratory data report and verbal or telephonic communication with patients. Patient's demographic characteristics (age, sex, diseases profile, comorbid condition) was documented from their prescription. Data collected were anonymised and information collected including demographic data, antidiabetic and other concomitant medication. Glycemic status of the patients were collected along with other biochemical parameters like blood urea, serum creatinine and lipid profile. This were noted as baseline parameter before addition of hydroxychloroquine in place of teneligliptin.

Study criteria

The inclusion criteria for this trial were: above18 years of age, both genders, T2DM patients, uncontrolled with teneligliptin bases multiple treatment regimen whose HbA_{1c} was in in the range of 7.5% to 9.5%, FBG level ≥ 126 mg/dl and PPBG level ≥ 200 mg/dl and body weight ≥ 60 kg. The exclusion criteria were as follows: subjects with a history of retinopathy, uncorrected visual acuity < 20/100, abnormal visual fields, difficulty examining the optic disc, or evidence of retinal pigment, epithelial abnormalities and history or risk of macular oedema. History of diabetic ketoacidosis and subjects with G6PD deficiency and pregnant or lactating women were also excluded. Eye scanning was done at baseline and after 24th week.

Study assessments

Estimation of blood glucose both fasting and postprandial along with blood urea and serum creatinine, lipid profiles analysis were done by auto analyser instrument in clinical biochemistry laboratory. We have considered the lab reports only from NABL accredit (from Govt. of India) pathological laboratories in India towards the accuracy of the reports. The HbA_{1c} was calculated by affinion's auto analyser of HbA_{1c} and alere's cartridge was used. The eGFR is generally considered to be the best index of renal function in health and disease. The eGFR was estimated by prediction equations that take into account serum creatinine concentration and some or all of the following variables: Age, sex, race and body size. The recommended equation by the national kidney foundation is that of the MDRD (Modified Diet in Renal Disease).

Statistical analysis

Descriptive analysis was done for the demographic details. Quantitative data of BMI, FBG, PPBG, HbA_{1c}, serum creatinine, eGFR, total cholesterol, triglyceride, LDL and HDL from baseline to 6 months after initiating hydroxychloroquine was analysed by two-tailed paired t-test for data following Gaussian distribution, while paired data not following the Gaussian distribution were analysed by nonparametric, Wilcoxon signed-rank test. Graph Pad Prism5 (version 5.01) statistical software was used for analysis. Statistical tests were considered significant if p-value was < 0.05 at confidence interval of 95%. The data was collected from the pre-existing hospitals records of the participating doctors and data audit was conducted for real world efficacy assessment retrospectively.

Results

Data of 500 patients were available for analysis. Table 1 shows the baseline demographic and clinical characteristics. The mean age of patients was 58.96 ± 5.4 years, among which 24% were more than 60 years of age. Out of the entire patient population 53% were males and among the entire selected population almost 69% had comorbid condition among which hypertension (61%) and dyslipidemia (41%) was most common. Antihypertensive and statin were the most commonly prescribed concurrent medications. Among antidiabetic drugs 40% of entire selected population were on teneligliptin + metformin + SU combination. In addition to teneligliptin, metformin and SU there were other therapies prescribed including α-glucosidase inhibitor, SGLT2i, thiazolidinedione and insulin.

Table 1. Baseline demographic and clinical characteristics of all patients

Patients characteristics	Number of patients, n (%)
Mean age (SD), y	58.96 ± 5.4
< 60	378 (76%)
≥ 60	122 (24%)
Male	265 (53%)
Female	235 (47%)
Family history of diabetes	348 (70%)
Duration of diabetes > 5 years	345 (69%)
HbA_{1c} distribution at baseline	
> 7.5 – < 8%	297 (59%)
≥ 8%	203 (41%)
Presence of comorbidities	
Hypertension	306 (61%)
Dyslipidemia	204 (41%)
Antidiabetic medications	
Teneligliptin + metformin + SU	200 (40%)
Teneligliptin + metformin + SU+ AGI	64 (13%)
Teneligliptin + metformin + SU+ SGLT2i	79 (16%)
Teneligliptin + metformin + SU + TZD	65 (13%)
Teneligliptin + metformin + SU+ insulin	92 (18%)
Other medications	
Antihypertensive agents	306 (61%)
Lipid-lowering agents	204 (41%)
Antiplatelet	159 (32%)
Antihypertensive + statin + antiplatelet	139 (28%)

SD — standard deviation; HbA_{1c} — glycated haemoglobin; AGI — α-glucosidase inhibitor; SU — sulfonylurea; TZD — thiazolidinedione; SGLT2i — sodium-glucose cotransporter-2 inhibitor

Change in HbA_{1c} (%) at 24 weeks

Table 2 shows the HbA_{1c} values at baseline, 24 weeks and change from baseline. Substituting from teneligliptin to hydroxychloroquine led to a further reduction of HbA_{1c} from 7.91 ± 0.33% to 6.81 ± 0.22%.

Table 2. Changes in physiological and biochemical parameters

Parameters	Before treatment (Mean ± SE)	After treatment (Mean ± SE)	p-value
BMI [kg/m^2]	25.76 ± 0.66	25.18 ± 0.67	0.049
FBG [mg/dl]	146.24 ± 9.44	116.37 ± 5.59	0.000
PPBG [mg/dl]	223.40 ± 12.23	166.51 ± 8.38	0.000
HbA_{1c} (%)	7.91 ± 0.33	6.81 ± 0.22	0.000
Blood urea	28.54 ± 0.60	28.37 ± 0.61	0.749
Serum creatinine [mg/dl]	0.97 ± 0.03	0.97 ± 0.01	0.967
eGFR	71.13 ± 3.49	70.46 ± 2.61	0.838
Total cholesterol [mg/dl]	181.28 ± 5.60	161.68 ± 4.44	0.023
Triglyceride [mg/dl]	152.64 ± 18.15	113.34 ± 12.71	0.043
LDL [mg/dl]	132.84 ± 9.35	120.14 ± 5.89	0.011
HDL [mg/dl]	38.98 ± 1.17	39.38 ± 1.32	0.000

BMI — body mass index; HbA_{1c} — glycated haemoglobin; eGFR — glomerular filtration rate; LDL — low density lipoprotein; HDL — high density lipoprotein

Table 3. Mean reduction in glycemic parameters compared to baseline

Category	After altering teneligliptin 20 mg with hydroxychloroquine 400 mg			
	FPG [mg/dl]	PPBG [mg/dl]	HbA_{1c} (%)	% of patients achieved, HbA_{1c} < 7%
Overall (n = 500)	–29.87 ± 8.9	–56.89 ± 9.2	–1.1 ± 0.17	62.59
Teneli + Met + SU (n = 200)	–31.21 ± 7.6	–56.29 ± 8.5	–1.1 ± 0.12	62.89
Teneli + Met + SU + AGI (n = 64)	–28.81 ± 8.4	–59.76 ± 7.9	–1.0 ± 0.16	60.39
Teneli + Met + SU + SGLT2i (n = 79)	–30,57 ± 9.5	–55.96 ± 9.6	–1.2 ± 0.14	68.85
Teneli + Met + SU + TZD (n = 65)	–29.17 ± 8.6	–55.98 ± 8.9	–1.0 ± 0.16	56.27
Teneligliptin + metformin + SU + insulin (n = 92)	–29.59 ± 9.4	–56.46 ± 9.7	–1.2 ± 0,17	65.64

Teneli — teneligliptin; Met — metformin; AGI — α-glucosidase inhibitor; SU — sulfonylurea; TZD — thiazolidinedione; SGLT2i — sodium-glucose cotransporter-2 inhibitor

Change in FBG, PPG at 24 weeks

At 24 weeks of treatment there is further change in FBG and PPBG from baseline after altering teneligliptin 20 mg to hydroxychloroquine 400 mg. FBW was reduced from 146.24 ± 9.44 mg/dl to 116.37 ± 5.59 and PPBG was reduced from 223.40 ± 12.23 mg/dl to 166.51 ± 8.38 mg/dl.

Patients achieving HbA_{1c} (%) target

At 24 weeks, the patients achieving target HbA_{1c} of < 7.0% with hydroxychloroquine 400 mg were 62.59%.

Change in blood urea, serum creatinine and eGFR

Change in blood urea (from 28.54 ± 0.60 mg/dl to 28.37 ± 0.61 mg/dl) was statistically non-significant. It has also been observed that after switch from teneligliptin to hydroxychloroquine there was no change in serum creatinine and eGFR.

Change in TC, TG, LDL and HDL

It has been seen that total cholesterol (TC), triglycerides (TG) and LDL levels were decreased and HDL increased after switching from teneligliptin 20 mg to hydroxychloroquine 400 mg. Total cholesterol reduced from 181.28 ± 5.60 mg/dl to 161.68 ± 4.44 g/dl, triglycerides reduced from 152.64 ± 18.15 mg/dl to 113.34 ± 12.71 mg/dl and LDL reduced from 132.84 ± 9.35 mg/dl to 120.14 ± 5.89 mg/dl.

Hydroxychloroquine effectiveness was analysed in different categories of the patient population who were on different type of drugs and mentioned in Table 3.

Eye check-up done to evaluate corrective lenses, it has been found that in all patients (n = 500) pupils are equal and reactive to light and accommodation, normal fundus oculi, no arteriovenous nicking, no retinopathy.

Discussion

In country like India where uncontrolled T2DM has very high prevalence, real world studies are of huge value and importance [12]. There were various studies performed which confirmed that most of the Indian patients fails to achieve treatment HbA_{1c} goals [13, 14] and their mean HbA_{1c} is much higher than the recommended standard [15]. Guidelines suggest the use of combination therapies including diverse oral antidiabetic drugs (OADs), acting via multiple mechanisms, to effectively manage hyperglycemia, while dealing with the challenges of the progressive nature of T2DM and monotherapy failure [14].

In this retrospective trial we have analysed 500 patients' data who have been treated in multiple hospital and private diabetes care setup across India and their biochemical test had carried out from a NABL accredit pathological laboratories towards authentic and accurate reports.

The addition of hydroxychloroquine in place of teneligliptin led to a significantly greater reduction of HbA_{1c} from baseline to 24 weeks in patients with type 2 diabetes mellitus receiving metformin and glimepiride with or without other antidiabetic therapy. These results also emphasize the importance of generally differentiating between the two drugs classes, since further improvement in glycaemic control can be achieved by substituting teneligliptin with hydroxychloroquine. There was further –1.1% reduction in HbA_{1c} after substituting teneligliptin with hydroxychloroquine.

In this study patients group was having average blood urea 28.54 mg/dl before the treatment and at the end of the treatment it was 28.37 mg/dl and also the change was statistically non-significant. It can be concluded from this finding that there was no effect on blood urea after hydroxychloroquine was prescribed in place of teneligliptin. It has also been noticed and recorded that after switch from teneligliptin to hydroxychloroquine there was no change in serum creatinine and eGFR. Therefore intensive treatment with hydroxychloroquine protecting kidney function.

A potent and significant control in lipid profile also been noticed after 6 month of treatment with hydroxychloroquine 400 mg. It has been seen that total cholesterol, triglycerides and LDL levels were decreased and HDL increased significantly. The similar result was also noticed in Pareek et al. [16], were there was a statistically significant fall within 6 months of treatment in TG, TC, LDL-C from baseline after addition of hydroxychloroquine 400 mg. This significant reduction in lipid profile also indicating the added advantage of hydroxychloroquine in reducing cardiovascular risk apart of providing tight glycemic control.

Hypertension and dyslipidemia are the most common two comorbid condition in this study, as majority of patients (72%) were hade this two comorbid condition. Even previously reported two studies performed in India are in accordance with this high prevalence. This retrospective data suggested that 41% patients are getting lipid lowering agents despite that there is further lipid lowering effect had seen with addition of hydroxychloroquine. 61% patients are receiving antihypertensive drugs, 32% antiplatelet and 28% statin, antiplatelet and statin combination to reduce cardiovascular risk in this diabetes patients.

There are some limitation of our study. Because for this open study design and as clinicians were selected antidiabetic drugs as per their judgement along with teneligliptin resulted in a possible imbalance favouring the hydroxychloroquine, although this did not seem to have a great impact. In addition, unlike in randomized controlled trials, reporting of AEs was based on a voluntary reporting scheme, which might have led to unnoticed or under-reported events.

Conclusion

In T2DM patients inadequately controlled on teneligliptin 20 mg along with combination of metformin and glimepiride with or without other antidiabetic therapy, substitute with hydroxychloroquine 400 mg may be a simple yet effective therapeutic option with clinical benefit beyond strict glycemic control without compromising patient's safety.

Contributors

All authors had full access to all data, and take responsibility for the integrity of the data and accuracy of analyses. All authors actively participated in the preparation of the manuscript and provided critical review at each step.

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