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Original Research Article

Comparison of the efficacy and safety of hydroxychloroquine versus teneligliptin as add on therapy in uncontrolled type 2 diabetes mellitus: a randomized, prospective and open labelled study

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ABSTRACT

Background: Type 2 Diabetes Mellitus (T2DM) is a multifactorial metabolic disorder characterized by chronic hyperglycaemia resulting from insulin resistance and β-cell dysfunction. Despite combination therapy with metformin and sulfonylureas, many patients fail to achieve optimal glycemic control, necessitating additional agents. Hydroxychloroquine (HCQS), an immunomodulatory drug, has shown potential antidiabetic and anti-inflammatory effects, while teneligliptin, a DPP-4 inhibitor, improves insulin secretion through incretin modulation.
Methods: A randomized, prospective, open-label study was conducted over three months in 100 T2DM patients aged 18–60 years with HbA1c ≥7.5%. Participants received either HCQS 400 mg once daily or teneligliptin 20 mg once daily, in addition to metformin and glimepiride. Fasting blood glucose (FBG), postprandial blood glucose (PPBG), and HbA1c were assessed at baseline, day 28, 56, and 84. Data were analyzed using ANOVA and unpaired t-tests, with $p<0.05$ considered significant.
Results: Both HCQS and teneligliptin significantly ($p<0.001$) reduced FBG, PPBG, and HbA1c levels from baseline. Comparative analysis showed a greater reduction in HbA1c with HCQS ($p<0.05$). No significant differences were observed in BMI or incidence of adverse effects between groups. Mild gastrointestinal symptoms were the most common adverse events.
Conclusions: Both HCQS and teneligliptin were effective and well-tolerated as add-on therapies in uncontrolled T2DM. HCQS demonstrated superior glycemic improvement, suggesting it as an economical and effective adjunct for better glycemic control in Indian patients.

Keywords: Type 2 diabetes mellitus, Hydroxychloroquine, Teneligliptin

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a heterogenous group of multifactorial disease of impaired carbohydrate, fat, protein imbalance including the derangement of the electrolytes characterized by prolonged hyperglycemic state, elevated fasting glucose levels associated with decreased amount of insulin release or absolute insulin

deficiency. Becoming a global burden, diabetes mellitus is one of the major metabolic disorders due to sedentary lifestyle and the prevalence rate is on a steep rise in developing economies.[1,2] T2DM, being the most prevalent type of diabetes and in India; it constitutes major part of the diabetes epidemic. According to the IDF Diabetes Atlas 2015, the prevalence of diabetes in India is report tbe 8.8%, although there are large variations across geographic areas and socioeconomic groups.[3]The management of T2DM involves lifestyle modifications like diet and exercise, oral anti diabetic drugs, and ultimately insulin is required exogenously to combat the destruction caused by the hyperglycemic state. Being a multifactorial morbidity, it is considered responsible for glucotoxicity, lipotoxicity, oxidative stress, endoplasmic reticulum stress, formation of amyloid deposits in the islets, etc. which tend to participate in the pathogenesis of the disease. The two most common oral anti-diabetic agents being used are metformin and sulphonylureas.[4]

It is well accepted fact that insulin resistance (IR) and islet β-cell function play a major part in the pathology of the disease. Over the last decade, numerous studies – prospective and cross-sectional, have confirmed the role of low-grade inflammation as a pathogenetic factor of T2DM. Increased levels of various inflammatory markers and mediators including fundamental markers like white blood cell count, C-reactive protein (CRP) to the more specific circulating cytokines like, interleukin-6 (IL-6), IL-1β, plasminogen activator inhibitor-1 (PAI-1), etc. are essential components in the development of the disease and mark the prognosis criteria.[5] However, Sulphonylureas are associated with side effects like hypoglycemia and weight gain. Despite combined therapy, none of them are able to preserve β-cell function and many patients with T2DM fail to reach target glycosylated hemoglobin (HbA1C<7.0%) level. Thereby, require insulin therapy eventually.[6]

Being a progressive disease, pharmacotherapy with a single agent would not be sufficient for long lasting glycemic control in the long run and addition of other anti-hyperglycemic agents is necessary.[7] DPP-4 inhibitors, after establishing a good well known safety profile provide good glycemic control with similar efficacy to SUs. No increase in cardiovascular risk has been shown large prospective study trials, so they have become an established therapy for T2DM.[8] Chronic use of anti-diabetic medications has made the researchers to hypothesize that their long-term use may ultimately be harmful to the remaining β-cells. Gliptins (also known as dipeptidyl peptidase-4 (DPP-4 inhibitors)) improve insulin secretion from the β-cells of the pancreas in response to increased blood glucose levels as compared to sulphonylureas which are associated with loss of the β-cells.[9] The insulin secretion is stimulated by secretion of higher levels of glucagon-like peptide-1 and glucose-dependent insulinotropic peptide are enzymes released from the intestine and are responsible for regulation of blood glucose levels. Additionally, the use of gliptins is associated with fewer hypoglycemic events.[10,11] Teneligliptin approaches towards potential outcomes in providing a safe anti diabetic option.[12] HCQS, used for treating the auto immune disorders may improve glucose tolerance and prevent diabetes. The drug has also been a long standing safe and inexpensive option. HCQS exerts its action by post receptor inhibition of insulin degradation and reduce the blood glucose levels.[13,14] Drug Controller General of India (DCGI) approved HCQS in 2014 for the management of T2DM as an adjuvant therapy to diet and exercise. HCQS was added to improve glycemic control in patients with T2DM on combination of sulphonylurea and metformin and even endorsed by RSSDI (Research Society for the Study of Diabetes in India) clinical practice recommendations for the management of type 2 diabetes mellitus 2017. It exerts the beneficial effect by slowing down the breakdown of internalized insulin-receptor complex along with reduction of pro-inflammatory markers ultimately leading towards a more achievable and sustained glycemic control. Due to paucity of literature, we propose to assess the efficacy and safety of HCQS as add on therapy in uncontrolled T2DM patients in comparison to standard DPP-4 inhibitors. The generated data and recommendations can be utilized in future for treating these patients.

METHODS

The study was conducted in the Outpatient Department of General Medicine, FMHS, SGT University after obtaining approval from the Institutional Ethics Committee. Written informed consent was obtained from all participants or their legally acceptable representatives prior to enrolment. This was a randomized, prospective, open-label study carried out over a period of three months i.e. from September 2020 to November 2020. A minimum of 100 subjects who fulfilled the predefined inclusion and exclusion criteria were enrolled. Eligible participants included male and female patients aged 18–60 years who had been receiving metformin 1000 mg and glimepiride 2 mg for at least two weeks prior to the initiation of the study, had a body weight of ≥60 kg, and had an HbA1c level of ≥7.5%. Participants were required to be willing to comply with all study-related procedures. Patients with type 1 diabetes mellitus, diabetic microvascular or macrovascular complications, a history of diabetic ketoacidosis, pregnant or lactating women, those with severe infections at the time of enrolment, clinically significant hepatic or renal disease, or any other condition deemed by the investigator to preclude participation were excluded from the study.

Study protocol

A predesigned case study form was used for collection of patient's details. (Table 1) On screening each patient will be subjected to a detailed medical history, demography and physical examination. Routine investigations of FBG, PPBG and HbA1c was done for confirmation. There was a 2-week run in period of diet control and treatment with

metformin 1000mg and glimepiride 2mg. All patients were subjected to randomization by random number table and allocated into two treatment groups; Group A and Group B which will be receiving following treatment regimens respectively: In both groups, all the drugs were given orally. Follow up visits included visit 2, visit 3 and visit 4 which were performed at 28th day (± 3 days), 54th day (± 3 days) and 84th day (± 3 days) as per the case record form (Annexure 1). At each visit complete physical examination will be carried out, including FBG and PPBG. HbA1c was examined only at the time of screening visit and visit 4.

Table 1: Treatment group of the study.

S. No.	Groups	Treatment
1	A	HCQS 400 mg + glimepiride 2 mg +metformin 1000 mg
2	B	Teneligliptin 20mg + glimepiride 2mg + metformin 1000mg per day

In addition, blood glucose level was measured at any time if a subject experiences symptom of hypoglycemia or if requested by treating physician. Any complication or Adverse drug reaction attributed to the treatment regimens was recorded in both the groups to assess the safety of the regimes. A blood sugar level below 70mg/dl is considered as hypoglycemia.

Physical parameters

BMI (body mass index): Body Mass Index is a simple calculation using a person's height and weight. The formula is BMI = kg/m^2 where kg is a person's weight in kilograms and m^2 is their height in meters squared.

A BMI of 25.0 or more is overweight, while the healthy range is 18.5 to 24.9. BMI applies to most adults 18-65 years.

BP: Was evaluated manually by the auscultatory method.

Glycemic parameters

FBG: Fasting arterial blood was taken and evaluated by the Accuchek glucometer.

PPBG: Arterial blood was taken and evaluated by the Accuchek glucometer.

HbA1p-C: Fasting venous blood was taken and calculated by the auto-analyzer, EM 30 (Transasia) by immunoturbidimetry method.

Statistical analysis

All the results were expressed in mean ± SD. The level of significance in more the two groups was evaluated by using One-way analysis of variance (ANOVA) followed by Bonferroni's post hoc test. However, significance level between HCQS and teneligliptin were analyzed by unpaired t-test. The $p < 0.05$ was considered as significant. The SPSS software version 20 was used for the statistical analysis.

RESULTS

Demographic distribution

The mean age of the patients was 45.39±6.22 and 46.85±5.18 years in HCQS and teneligliptin respectively, with mean duration of diabetes of more than 7 years. Mean body weight was 79.16±6.52kg and 80.99±9.47kg respectively in HCQS and teneligliptin group (Table 2).

Effect of HCQS and teneligliptin treatment on BMI

No significant difference has been found in BMI at baseline as well as all the time point (28th, 56th and 84th day) (Table 3). Similarly, the comparative analysis also did not show any significant difference between HCQS and teneligliptin treatment groups.

Effect of HCQS and teneligliptin treatment on FBG level

The mean baseline FBG levels have not shown significant difference between HCQS and teneligliptin treatment group. The significant ($p<0.001$) reduction in fasting blood glucose level was found in all the time points at 28^{th}, 56^{th} and 84^{th} day as compared to baseline blood glucose level in both HCQS and teneligliptin treatment groups (Table 4). However, in comparative analysis, no significant difference was found in both the treatment group at all the time points (28^{th}, 56^{th} and 84^{th} day) (Figure 1).

Effect of HCQS and teneligliptin treatment on PPBG level

The mean baseline PPBG levels have not shown significant difference between HCQS and teneligliptin treatment group. The significant ($p<0.001$) reduction in PP blood glucose level was found in all the time points at 28^{th}, 56^{th} and 84^{th} day as compared to baseline blood glucose level in both HCQS and teneligliptin treatment groups (Table 5) However, no significant difference was found in both the treatment group at all the time points in the comparative analysis, (Figure 2).

Table 2: Profile of subjects enrolled in the study.

Characteristics	HCQS group (n=50)	Teneligliptin (n=50)
Age (years)	45.39±6.22	46.85±5.18
Weight (kgs)	79.16±6.52	80.99±9.47
Gender (M/F)	30/20	31/19
Family history (Y/N)	36/14	38/12
Duration of diabetes (years)	7.5±2.15	8.2±3.16
HBA1C (%)	8.35±0.55	8.19±0.39
Fasting blood glucose (mg/dl)	173.54±29.49	181.66±38.45
Post prandial blood glucose (mg/dl)	241.15±32.17	247.6±27.16
Presence of comorbidities		
Hypertension (Y/N)	43/7	42/8
Dyslipidaemia (Y/N)	36/14	38/12

Each value represents mean ± SD, HCQS: Hydroxychloroquine.

Table 3: Effect of HCQS and teneligliptin treatment on BMI of type-2 diabetic patients.

S. no.	Treatment group	Baseline	28th days	56th days	84th days
1	HCQS 400 mg + glimepiride 2 mg +metformin 1000 mg	27.74±1.59	25.61±1.52	25.37±1.54	25.22±1.51
2	Teneligliptin 20mg + glimepiride 2mg + metformin 1000mg per day	24.85±1.22	24.82±1.23	24.75±1.27	24.70±1.24

Each value represents mean ± SD, HCQS: Hydroxychloroquine.

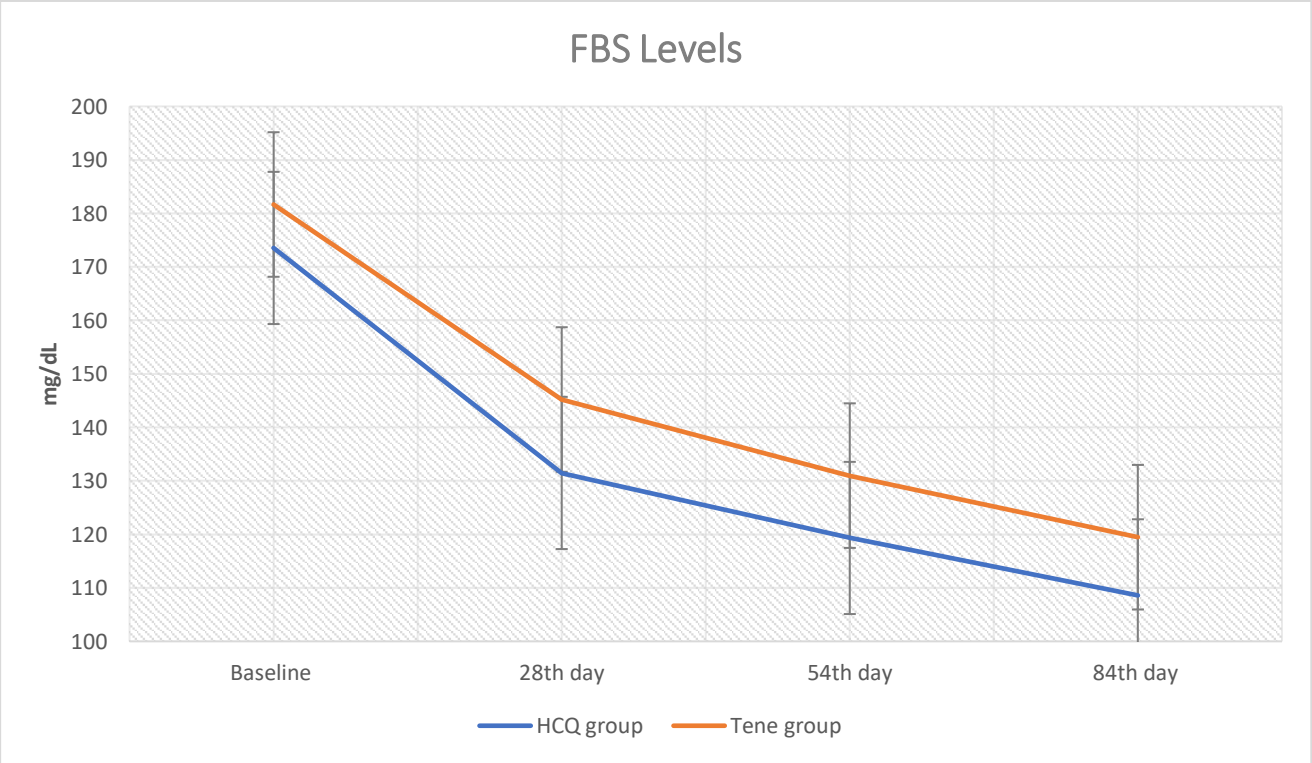

Figure 1: Comparative analysis of HCQS and teneligliptin treatment on FBG in type-2 diabetic patients. Each value represents mean ± SD, HCQS: hydroxychloroquine.

Table 4: Effect of HCQS and teneligliptin treatment on FBG of type-2 diabetic patients.

S. no.	Treatment group	Baseline	28th days	56th days	84th days
1	HCQS 400 mg + glimepiride 2 mg +metformin 1000 mg	173±29.49	131.48±21.57 a***	119.33±14.68 a***	108.59±13.54 a***
2	Teneligliptin 20mg + glimepiride 2mg + metformin 1000mg per day	181.66±38.48	145.21±18.69 a***	130.98±17.20 a***	119.47±13.51 a***

Each value represents mean ± SD, ***P<0.001, 'a' as compared to baseline, HCQS: Hydroxychloroquine.

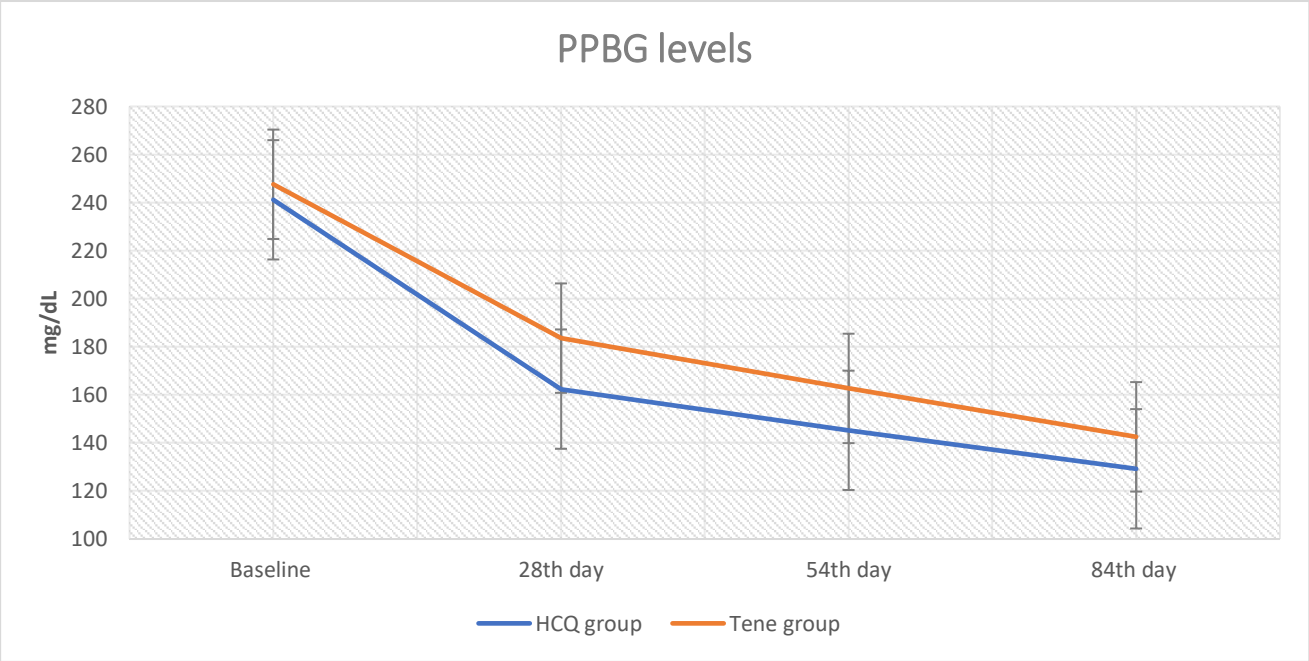

Figure 2: Comparative analysis of HCQS and teneligliptin treatment on PPBG in type-2 diabetic patients. Each value represents mean ± SD, HCQS: hydroxychloroquine.

Table 5: Effect of HCQS and teneligliptin treatment on PPBG of type-2 diabetic patients.

S. no.	Treatment group	Baseline	28th days	56th days	84th days
1	HCQS 400 mg + glimepiride 2 mg +metformin 1000 mg	241.15±32.17	162.37±26.15^{a***}	145.22±21.69^{a***}	129.16±20.48 ^{a***}
2	Teneligliptin 20mg + glimepiride 2mg + metformin 1000mg per day	247.60±27.16	183.59±24.84^{a***}	162.66±21.08^{a***}	142.51±14.57 ^{a***}

Each value represents mean ± SD, ***P<0.001, 'a' as compared to baseline, HCQS: Hydroxychloroquine.

Table 6: Effect of HCQS and teneligliptin treatment on HbA1C level of type-2 diabetic patients.

S. no.	Treatment group	Baseline	84th days
1	HCQS 400 mg + glimepiride 2 mg +metformin 1000 mg	8.35±0.55	6.81±0.33^{a***}
2	Teneligliptin 20mg + glimepiride 2mg + metformin 1000mg per day	8.29±0.33	7.15±0.41^{a***}

Each value represents mean ± SD, ***P<0.001, 'a 'as compared to baseline, HCQS: Hydroxychloroquine.

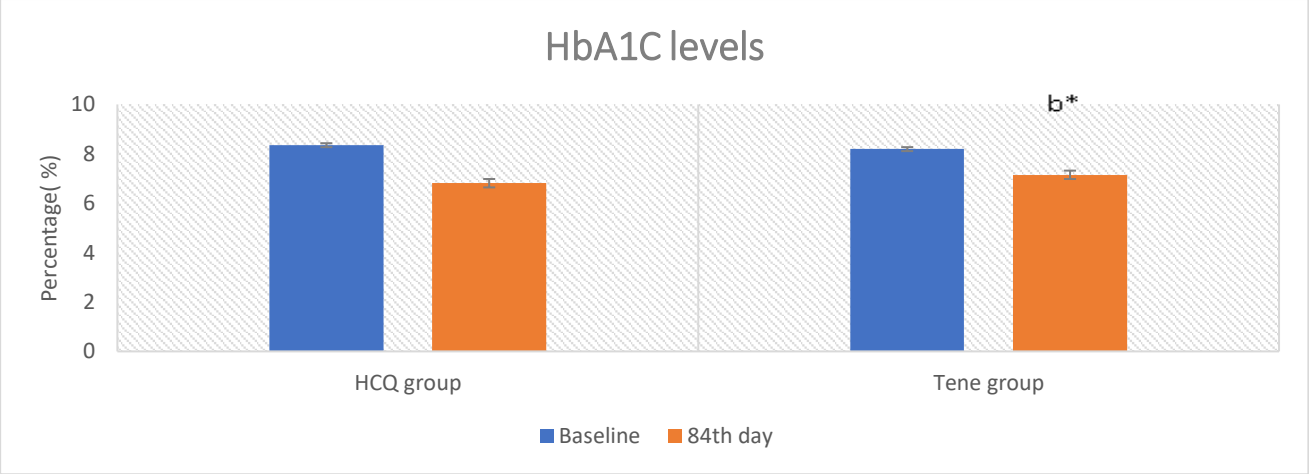

Figure 3: Comparative analysis of HCQS and teneligliptin treatment on HbA1C in type-2 diabetic patients. Each value represents mean ± SD, *p<0.05, 'b' as compared to HCQS treatment group, HCQS: hydroxychloroquine.

DISCUSSION

Diabetes being the major cause of morbidity in the 21st century tops the chart in affecting the vulnerable section of the society. Studies have found the prevalence of diabetes and prediabetes in India to be as high as 7.3% and 10.3% respectively with nation-wide projection of 77.2 million people with prediabetes and 69.2 million with diabetes as per Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) findings. Insulin resistance (IR), impaired insulin secretion and later islet β-cell failure are the prominent features of T2DM. The proinflammatory cytokines play a central role in the development of microvascular diabetic complications such as nephropathy, retinopathy and neuropathy have been indicated by various studies and the role of inflammation has been ascertained in T2DM pathogenesis. Atherosclerosis being a major complication in T2DM gets accelerated by the inflammatory progresses leading towards cardiovascular diseases and ultimately increasing cause of mortality in the patientsAnti-inflammatory therapies are being worked upon in the treatment of chronic disorders such as T2DM and cardiovascular diseases.[3] The first line agents or anti-hyperglycemic drugs like metformin and sulfonylureas prove to be an effective and easy option for the patients as they are cost effective too. In due course of time, these agents lose their effectiveness and a third line drug has to be added for good glycemic control and to delay complications. Majority of new treatment options like GLP1 agonists, insulin analogs and SGLT2 inhibitors are costly, considering they are still under patent. The thiazolidinedione class of drugs is associated with adverse effects like fluid retention and weight gain that may result in or exacerbate edema and congestive heart failure. For the management of uncontrolled T2DM safe and inexpensive treatment options are needed.

As the role of inflammation is established in T2DM pathogenesis, the drug should not only have antihyperglycemic effects but should also exhibit anti-inflammatory properties to reduce the progression and complications of T2DM. Drugs targeting inflammation, acting at different stages of the inflammatory cascade are of current interest. Hydroxychloroquine being an immunomodulator has established its role as a potential anti-inflammatory drug. It is also being used for the treatment of diabetes mellitus which showed significant improvement of the lipid profile, insulin levels and substantial diminution of Hba1c, fasting plasma glucose and post prandial blood glucose levels.[15] Enhancement in insulin sensitivity and adiponectin levels and reduction in lysosomal degradation of the internal insulin-insulin receptor complex are some of the currently studied mechanisms for the anti-hyperglycemic effect of hydroxychloroquine.[16]

Gliptins, are considerable and efficacious antidiabetic class of agents that alter beta cell function, suppressing glucagon which results in improved post-prandial and fasting hyperglycemia. Their action is to augment the incretin system (GLP-1 and GIP) preventing their metabolism by dipeptidyl peptidase-4 (DPP-4). They are safe and efficacious agents which do not cause significant hypoglycemia making them a unique class of drugs.[17]

Overall assessment of safety demonstrated that both hydroxychloroquine and teneligliptin were well tolerated in this observational real-world efficacy and safety assessment study. No meaningful differences were found in the adverse experience profiles between hydroxychloroquine and teneligliptin treatments. There was a very low incidence of hypoglycemia with hydroxychloroquine that was similar to teneligliptin. Slightly higher, but not statistically significant, incidences of gastritis, constipation, and diarrhea were reported with hydroxychloroquine, but these events were generally mild or moderate.[18] Incidences of nausea, vomiting, mild gastrointestinal disturbances like abdominal fullness and constipation were reported in a few cases.

In reference with other study, this report statistically proves the better role of hydroxychloroquine as compared with teneligliptin and signifies its effectiveness.[5] Both teneligliptin and hydroxychloroquine are available in India at economical prices which can be afforded by a patient who are financially unstable or belong to the middle-class.

CONCLUSION

Treatments with hydroxychloroquine and teneligliptin resulted in significant reductions in the glycemic parameters. The results with hydroxychloroquine exhibited greater effectiveness in improving FBG, PPBG and HbA1c than teneligliptin. In conclusion, hydroxychloroquine exhibited better outcomes with OD dose of 400mg as compared to Teneligliptin 20mg in reduction of the HbA1c in Indian Type 2 diabetic patients, although the difference is modest.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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