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Antihyperglycemic properties of hydroxychloroquine in patients with diabetes: Risks and benefits at the time of COVID-19 pandemic

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Abstract

The antimalarial drug hydroxychloroquine (HCQ) has long been used as a disease-modifying antirheumatic drug for the treatment of several inflammatory rheumatic diseases. Over the last three decades, various studies have shown that HCQ also plays a role in the regulation of glucose homeostasis. Although the mechanisms of action underlying the glucose-lowering properties of HCQ are still not entirely clear, evidence suggests that this drug may exert multifaceted effects on glucose regulation, including improvement of insulin sensitivity, increase of insulin secretion, reduction of hepatic insulin clearance, and reduction of systemic inflammation. Preliminary studies have shown the safety and efficacy of HCQ (at a dose ranging from 400 to 600 mg/day) in patients with type 2 diabetes over a short-term period. In 2014, HCQ has been approved in India as an add-on hypoglycemic agent for patients with uncontrolled type 2 diabetes. However, large randomized controlled trials are needed to establish the safety and efficacy profile of HCQ in patients with type 2 diabetes over a long-term period. With regard to the COVID-19 pandemic, several medications (including HCQ) have been used as off-label drugs because of the lack of proven effective therapies. However, emerging evidence shows limited benefit from HCQ use in COVID-19 in general. The aim of this manuscript is to comprehensively summarize the current knowledge on the antihyperglycemic properties of HCQ and to critically evaluate the potential risks and benefits related to HCQ use in patients with diabetes, even in light of the current pandemic scenario.

KEYWORDS
antidiabetic medications, COVID-19, diabetes mellitus, hydroxychloroquine, SARS-CoV-2

Highlights
- Hydroxychloroquine (HCQ) has been shown to exert antihyperglycemic properties by virtue of potential multifaceted effects on glucose homeostasis,

including improvement of insulin sensitivity, increase of insulin secretion, and reduction of systemic inflammation.
- Preliminary studies have shown the safety and efficacy of HCQ as an antihyperglycemic agent in type 2 diabetes over a short-term period.
- A careful risk-benefit assessment of HCQ is critical for a cautious use of this drug in diabetic patients, particularly in light of the current COVID-19 pandemic.

1 | HYDROXYCHLOROQUINE AS AN ANTIHYPERGLYCEMIC AGENT

Since the 1940s, the antimalarial drugs chloroquine and hydroxychloroquine (HCQ) have been used as disease-modifying antirheumatic drugs (DMARDs) for the treatment of several inflammatory rheumatic diseases, including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).[1] Importantly, HCQ has shown a good safety and tolerability profile in most patients, even during pregnancy and breastfeeding.[1,2]

Intriguingly, a growing body of evidence coming from studies conducted over the last three decades suggests that HCQ also plays a role in the regulation of glucose homeostasis in individuals with and without diabetes.[3] Although the exact mechanisms of action underlying the glucose-lowering properties of HCQ are still not entirely clear and may differ between patients with and without diabetes, preclinical and clinical data suggest that HCQ could exert multifaceted effects on glucose homeostasis, namely improvement of insulin sensitivity, increase of insulin secretion, reduction of hepatic insulin clearance and intracellular insulin and insulin-receptor complex degradation, increase of adiponectin levels, reduction of systemic inflammation, and/or reduction of inflammation-induced insulin resistance in adipocytes and skeletal muscle cells.[3-5] In this regard, a randomized study is currently underway at Washington University (MetaHcQ, Metabolic Effects of Hydroxychloroquine; ClinicalTrials.gov Identifier: NCT02026232) to evaluate the effects of 4-week HCQ administration (at a dose of 400 mg/day) on insulin sensitivity (determined by hyperinsulinemic euglycemic clamp), fasting blood glucose, lipid profile, and serum biomarkers of inflammation in subjects with type 2 diabetes mellitus (T2D).

Remarkably, several studies demonstrated that HCQ use is associated with a significantly reduced risk of developing diabetes in nondiabetic subjects with inflammatory rheumatic diseases, including RA,[6-8] SLE,[9] psoriasis,[8] and Sjögren syndrome.[10]

In the early 1990s, an Italian 6-month randomized, placebo-controlled trial conducted by Quatraro et al[11] in 38 T2D subjects first showed that the addition of HCQ (600 mg/day) to glibenclamide or insulin led to a significant reduction in glycated hemoglobin (HbA1c), accompanied by a 30% reduction in daily insulin dose among patients on insulin therapy. Thereafter, a Canadian randomized, placebo-controlled trial conducted in 135 obese patients with T2D refractory to sulfonylureas showed that the addition of HCQ (up to a maximum of 300 mg bid) reduced HbA1c by an absolute amount of 1.02% more than placebo after 6 months.[12] No significant HCQ-related side effects were reported in these studies, except for a severe hypoglycemic episode that occurred in one patient treated with HCQ in combination with insulin.[11] Moreover, a retrospective study conducted in diabetic patients with concomitant rheumatic diseases (RA and SLE) showed that HCQ, when compared to methotrexate, was associated with a significantly greater reduction in HbA1c from pretreatment baseline to its lowest value within 12 months of treatment initiation.[13]

More recently, a 24-week prospective randomized trial[14] and two real-world, prospective observational studies of short duration (up to 24-48 weeks)[5,15] conducted in India have shown that the use of HCQ (400 mg/day) as an add-on treatment in patients with T2D uncontrolled on a combination of two or more oral hypoglycemic agents (including metformin, sulfonylureas, pioglitazone, DPP-4 inhibitors, SGLT2 inhibitors, and alpha-glucosidase inhibitors) was well tolerated and led to a significant improvement of glucose control (assessed by HbA1c, fasting- and postprandial blood glucose) from baseline (without occurrence of severe hypoglycemia).

In India, diabetes has reached epidemic proportions over the last years and newer antidiabetic drugs pose affordability challenges due to their high cost. Based on the aforementioned preliminary results, HCQ (at a dose of 400 mg/day) has been approved in 2014 by the Drug Controller General of India (DCGI) as a third-line (add-on) hypoglycemic agent for patients with inadequately controlled T2D despite lifestyle management associated with sulfonylurea and metformin combination therapy.[16,17] Thereafter, a vibrant debate about HCQ safety in T2D has arisen within the Indian scientific community.[18-21]

2 | ANTIHYPERGLYCEMIC PROPERTIES OF HCQ: CURRENT MECHANISTIC EVIDENCE

Animal and human studies support the existence of different molecular mechanisms underlying the antihyperglycemic properties of HCQ (and chloroquine). A study conducted by Halaby et al[22] in cultured rat muscle cells and in a rat model of insulin resistance demonstrated that chloroquine can promote insulin-mediated glucose uptake and glycogen synthase activity by activating Akt. In 1991, Powrie et al[23] conducted a randomized, placebo-controlled trial in 20 patients with T2D (referred to as "non-insulin-dependent diabetes mellitus") who were not receiving any antidiabetic medication and were adopting dietary measures only for diabetes management. The authors performed a hyperinsulinemic euglycemic clamp before and after a 3-day treatment with chloroquine (250 mg administered four times daily) or placebo, using a stable isotopically labeled D-glucose to calculate hepatic glucose production (Ra, rate of glucose appearance) and glucose utilization (Rd, rate of glucose disappearance). Notably, chloroquine led to a significant reduction in fasting plasma glucose and a significant rise in the total amount of exogenous glucose required to maintain euglycemia during the whole experiment, because of an increase in Rd (without changes in Ra). Also, chloroquine administration resulted in a 39% reduction in metabolic clearance rate of insulin at low-dose insulin infusion. More important, fasting C-peptide levels significantly increased throughout the study after chloroquine treatment, despite the initially lower plasma glucose values. A decreased feedback inhibition of C-peptide secretion was also reported during low- and high-dose insulin infusion (by 9.1% and 10.6%, respectively).[23] Overall, these data suggest that chloroquine can improve fasting glucose levels in subjects with T2D by (a) increasing peripheral glucose disposal (as evidenced by the increased overall glucose infusion rate required to maintain euglycemia, associated with an increase in Rd), (b) reducing hepatic insulin clearance, and (c) increasing endogenous insulin secretion both in the fasting state and during hyperinsulinemia. The assumption of the authors that chloroquine has a direct insulinotropic effect on pancreatic beta cells is strengthened by the fact that C-peptide has a negligible hepatic clearance and approximately half of the produced C-peptide is metabolized by the kidneys; in particular, the majority of total C-peptide produced is degraded via peritubular uptake and approximately 5% is excreted unchanged in the urine.[24,25] However, these findings cannot be directly translated to HCQ, even though chloroquine and HCQ display similar pharmacodynamic properties.[1] Thus, further investigation is warranted in this direction.

A study conducted by Emami et al[26] in diabetic rats showed that HCQ increased circulating insulin levels and reduced blood glucose levels in a concentration-dependent manner. In a subsequent study, the same authors found that HCQ can inhibit cytosolic insulin-metabolizing enzyme and intracellular insulin degradation in rat liver cells.[27]

In 2012, Mercer et al[28] showed that HCQ therapy (at a dose of 6.5 mg/Kg/day) for 6 weeks was associated with a significantly increase in insulin sensitivity index (ISI)—assessed by a 120-minutes oral glucose tolerance test (OGTT)—along with trends toward reduced insulin resistance (determined by homeostatic model assessment of insulin resistance [HOMA-IR]) in nondiabetic obese subjects without systemic inflammatory conditions. Thereafter, Wasko et al[4] confirmed similar results in a 13-week randomized, placebo-controlled study, showing that HCQ (400 mg/day) improved both beta-cell function (determined by the disposition index) and ISI (assessed by intravenous glucose tolerance test) in nondiabetic overweight or obese subjects. At variance with these findings, a randomized, placebo-controlled crossover trial conducted by Solomon et al[29] in nondiabetic subjects with stable RA showed that treatment with HCQ for 8 weeks (at a dose of 6.5 mg/Kg/day and not to exceed 600 mg/day) produced no significant change in ISI (assessed by 120-minutes OGTT) and insulin resistance (assessed by HOMA-IR) compared to placebo. These results may indicate that HCQ can prevent development of diabetes in patients with inflammatory rheumatic diseases—as it has been widely demonstrated [6-10] through additional mechanisms other than improvement in insulin sensitivity.

HCQ is a well-known anti-inflammatory and immunomodulatory agent able to reduce the production of proinflammatory cytokines and is therefore used as a DMARD for the treatment of several inflammatory rheumatic diseases.[1,30] With regard to the anti-inflammatory effects of HCQ in T2D, Amit Gupta[5] has recently shown that diabetic patients with higher baseline levels of high-sensitivity C-reactive protein (hs-CRP >3 mg/L) exhibited a more pronounced, although not significant, improvement in glucose control from baseline to 48 weeks after the initiation of HCQ therapy, as compared to patients with lower baseline levels of hs-CRP ($\leq$ 3 mg/L). Furthermore, patients with higher baseline hs-CRP levels also exhibited higher (although not significant) baseline levels of HbA1c and fasting and postprandial glucose levels.[5] The previously mentioned study by Wasko et al[4] conducted in nondiabetic overweight or obese subjects also found that HCQ (at a dose of 400 mg/day) significantly

increased plasma levels of the adipokine adiponectin, which plays a key role in insulin resistance and metabolic syndrome by exerting anti-inflammatory actions and increasing insulin sensitivity.[31-33]

Importantly, HCQ use up to 24 weeks (at a dose of up to 600 mg/day) in patients with T2D has also led to an improved lipid profile, which consisted of a significant reduction in total cholesterol, low-density lipoprotein (LDL) cholesterol, and non-high-density lipoprotein cholesterol in different studies.[12,14,15] A randomized, placebo-controlled crossover trial also found a significant reduction in total cholesterol and LDL-cholesterol after 8 weeks of HCQ therapy (at a dose of 6.5 mg/Kg/day and not to exceed 600 mg/day) in nondiabetic patients with RA.[29] Nevertheless, it is still not clear whether the potential lipid-lowering properties of HCQ may depend on its anti-inflammatory actions rather than on other HCQ-related mechanisms.

Interestingly, Type 1 Diabetes (T1D) TrialNet international network is currently investigating the potential ability of HCQ to prevent or delay the progression from normal glucose tolerance to impaired glucose tolerance or symptomatic T1D in subjects with islet autoimmunity, who are at increased risk of developing T1D (ClinicalTrials.gov Identifier: NCT03428945). Therefore, participants enrolled in this study are subjects in stage 1 (islet autoimmunity) of T1D pathophysiology.[34] However, the current lack of data on safety and efficacy of HCQ in patients with established T1D does not allow for any conclusion concerning the use of this drug in T1D.

Altogether, these findings suggest that HCQ regulates glucose homeostasis by virtue of multifaceted effects, which may allow for classifying this drug as an anti-diabetic medication potentially acting as an insulin-sensitizing agent (insulin sensitizer), an anti-inflammatory agent, and/or an insulinotropic agent (secretagogue) (Figure 1). Since chronic low-grade inflammation and islet inflammation have been linked to insulin resistance and beta-cell dysfunction in T2D, respectively,[33,35-37] the anti-inflammatory actions of HCQ may be at the interface between its insulin-sensitizing effects and its insulinotropic properties. On the basis of preclinical data in animals, HCQ appears to have the ability to (a) inhibit intracellular insulin and insulin-receptor complex degradation, (b) increase circulating
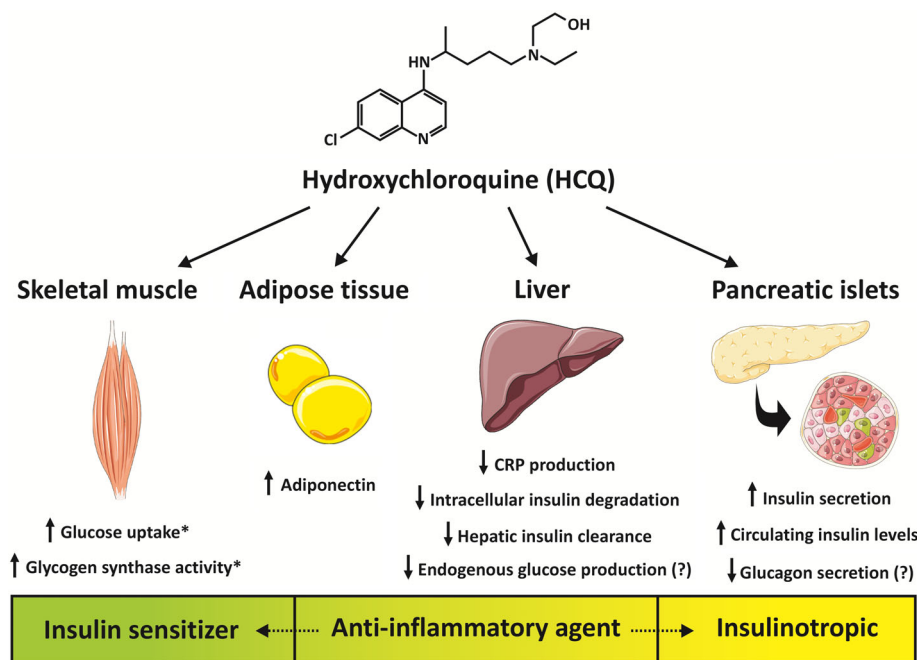
FIGURE 1 Potential molecular mechanisms underlying the hydroxychloroquine-mediated antihyperglycemic effects. Evidence from animal and human studies conducted in subjects with and without diabetes suggests that hydroxychloroquine regulates glucose homeostasis by virtue of multifaceted effects, including increase of insulin secretion, improvement of insulin sensitivity, reduction of hepatic insulin clearance and intracellular insulin and insulin-receptor complex degradation, increase of adiponectin levels, reduction of systemic inflammation, and/or reduction of inflammation-induced insulin resistance in adipocytes and skeletal muscle cells. Altogether, these actions may allow for classifying hydroxychloroquine as an antidiabetic agent which acts as an insulin-sensitizing agent, an anti-inflammatory agent and/or an insulinotropic agent (secretagogue). Since chronic low-grad inflammation and islet inflammation have been linked to insulin resistance and beta-cell dysfunction in type 2 diabetes, respectively, the anti-inflammatory actions of hydroxychloroquine may be at the interface between its insulin-sensitizing actions and its insulinotropic properties. *Effects observed with chloroquine in a rat model of insulin resistance. Abbreviations: CRP, C-reactive protein

insulin levels, (c) reduce blood glucose levels, and (d) promote glucose uptake and glycogen synthase activity in skeletal muscle cells. Thus, it is tempting to speculate that HCQ is able to inhibit glucagon secretion by pancreatic alpha cells and/or glucagon action in the liver. Additionally, it is still not clear whether the putative effect of HCQ on endogenous insulin secretion is mediated by a direct stimulatory effect on beta cells and/or by indirect effects involving the reduction of islet inflammation and/or the reduction of glucotoxicity- and lipotoxicity-related beta-cell dysfunction following the improvement in metabolic control. Moreover, the lack of severe hypoglycemic episodes observed across the studies investigating the use of HCQ as an antidiabetic medication in T2D (even when HCQ was administered in combination with sulfonylureas) may underlie a putative glucose-dependent insulin secretion mechanism mediated by HCQ. Yet, the occurrence of severe hypoglycemic episodes cannot be excluded in these studies, because they did not employ continuous glucose monitoring. Notwithstanding, we believe that all these speculations and unanswered questions may prompt researchers to conduct future mechanistic studies in order to elucidate the exact mechanisms underlying the antihyperglycemic properties of HCQ in both subjects with and without diabetes.

3 | POTENTIAL RISKS OF HCQ USE IN PATIENTS WITH DIABETES

Even though HCQ is considered as one of the safest DMARD and has been widely used for the treatment of RA and SLE,[1] data on long-term safety and efficacy of HCQ in diabetes are still lacking. Therefore, the use of HCQ in patients with diabetes should be carefully evaluated, particularly in subjects with established microvascular and/or macrovascular complications.

The most dreaded complication deriving from HCQ use is retinal toxicity.[1] However, current evidence suggests that high-dose and long-term (>5 years) use represent the most important predictors of HCQ-induced retinopathy.[1] Therefore, the American Academy of Ophthalmology recommends a maximum HCQ dose of ≤5 mg/kg actual body weight per day to markedly minimize the risk of retinopathy.[38] Also, HCQ-mediated cardiotoxic effects (including potentially lethal heart rhythm disorders, such as prolonged QT interval, ventricular arrhythmia, and Torsades de Pointes) have been reported.[1,39-41] Thus, baseline electrocardiography to evaluate for prolonged QT interval is advisable prior to and following the initiation of HCQ, particularly in high-

risk subjects such as hospitalized patients and individuals taking other QT interval-prolonging drugs (eg, macrolides such as azithromycin, quinolones, antihistamines, antiviral and antifungal drugs, anti-arrhythmic medications, etc.).[2,42-44] Risk factors for potentially lethal cardiac arrhythmias induced by HCQ include (a) coexisting cardiac conditions such as cardiomyopathy, left ventricular dysfunction, ventricular hypertrophy, coronary artery disease, heart failure, or bradycardia; (b) history of bradycardia, prolonged QT interval, ventricular arrhythmia, or (unexplained) syncope; (c) family history of premature sudden cardiac death or cardiac ion channelopathies; (d) pacemaker and implantable cardioverter-defibrillator use; (e) electrolyte abnormalities such as hypokalemia and hypomagnesemia; (f) genetic and autoimmune channelopathies; (g) systemic inflammation; and (h) concomitant use of azithromycin or other QT interval-prolonging agents.[42-51]

With regard to the renal function, chronic kidney disease can result in reduced HCQ clearance, increased drug bioavailability and subsequent augmented risk of HCQ-related side effects.[1] Furthermore, certain drugs (such as tamoxifen, glycosides, methotrexate, and ciclosporin) can influence the pharmacokinetics of HCQ.[1] These drug interactions can increase the risk of HCQ-related side effects and therefore require careful consideration.

Besides the well-known contraindications to HCQ use (including known hypersensitivity to 4-aminoquinoline compounds),[2,44] other conditions or circumstances under which HCQ should be contraindicated or used with caution in the context of diabetes include the following:

- Preexisting retinopathy/maculopathy, history or risk for macular edema, and concomitant use of other oculotoxic agents.[38,52]
- Diabetes complicated by hypoglycemia unawareness, repeated episodes of severe hypoglycemia and/or malnutrition, because of the potential risk for severe hypoglycemic episodes. Although HCQ-induced severe hypoglycemia has mainly been documented in nondiabetic subjects,[53-55] there have been a few reports of severe hypoglycemic episodes occurred with the use of HCQ in patients with newly diagnosed T2D[56] and established T2D treated with multiple daily injection insulin therapy.[11,57]
- Preexisting cardiomyopathy or heart failure, because of the possible risk of HCQ-related cardiotoxicity.[43]
- Preexisting myopathy and/or neuropathy, because of the potential risk of HCQ-induced neuromyotoxicity.[58-63]
- Glucose-6-phosphate dehydrogenase (G6PD) deficiency, because of the potential increased risk of HCQ-related hemolysis crisis.[64] Interestingly,

Heymann et al[65] found a significantly higher proportion of G6PD-deficient patients among the diabetic population aged 45-64 years. However, a large retrospective study of 275 patients with rheumatic diseases examined the relationship between HCQ use and hemolytic anemia in G6PD-deficient patients, showing that 4% of patients had G6PD deficiency (11 subjects, all African American) and only two of them had episodes of hemolysis that occurred while not taking HCQ.[66] Based on these findings, authors did not support routine measurement of G6PD levels or withholding HCQ therapy in African American patients with G6PD deficiency.[66]

Importantly, a proper risk-benefit assessment of HCQ use in diabetic patients should also be considered in relation to the current coronavirus disease 2019 (COVID-19) pandemic caused by the novel coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2)[67,68] and declared a global pandemic by the World Health Organization on 11 March 2020.

So far, several medications (including HCQ and chloroquine) have been used in hospital settings as off-label drugs for COVID-19 because of the current lack of proven effective therapies.[2,45] However, a recent observational study conducted on 1376 consecutive hospitalized patients with COVID-19 and moderate-to-severe respiratory illness showed that HCQ did not have a significant impact on the risk of intubation or death over a median follow-up period of 22.5 days.[69,70] Despite the observational design of this study, these findings dot not support HCQ use for treatment of COVID-19 outside randomized, placebo-controlled trials.[70] Indeed, the Food and Drug Administration has recently cautioned against the use of HCQ or chloroquine for COVID-19 outside of hospital- or clinical trial settings due to the risk of potentially lethal cardiac arrhythmias.[71] Nonetheless, several randomized controlled trials are now actively recruiting participants worldwide to assess the safety and efficacy of HCQ (alone or in combination with other drugs) for prophylaxis and treatment of COVID-19.[72]

Importantly, diabetes has reached epidemic proportions over the last years,[73] affecting approximately 463 million people worldwide according to recent estimates.[74] Also, emerging evidence suggests that diabetes represents one of the most prevalent comorbidities in patients with COVID-19,[75-77] as well as a major risk factor for a worse prognosis of the disease.[76-83] In light of these remarks, a preemptive and careful evaluation of all the potential risks and benefits related to HCQ is critical for a proper and cautious use of this drug in subjects with diabetes, particularly in the context of COVID-19.

4 | CONCLUSIONS

Over the last decades, several studies have shown that HCQ plays an important role in the regulation of glucose homeostasis through multifaceted effects, including improvement of insulin sensitivity, increase of insulin secretion, reduction of hepatic insulin clearance and intracellular insulin and insulin-receptor complex degradation, and reduction of systemic inflammation, among others (Figure 1). Different studies have shown the safety and efficacy of HCQ use (at a dose ranging from 400 to 600 mg/day) in patients with T2D over a short-term period (up to 18 months).[5,11,12,14,15,84] In 2014, HCQ (at a dose of 400 mg/day) has been approved in India as an add-on hypoglycemic agent for patients with inadequately controlled type 2 diabetes despite lifestyle management associated with sulfonylurea and metformin combination therapy. Nevertheless, concerns on long-term safety of HCQ in patients with T2D still persist due to the lack of robust data. Thus, large randomized controlled trials of long duration are warranted to establish the long-term safety and efficacy of this drug in the context of T2D. With regard to the current pandemic scenario, emerging evidence shows that patients with diabetes have a greater risk for adverse outcomes following COVID-19 infection. Although findings from clinical studies have suggested limited benefit from HCQ in COVID-19 in general,[85] several randomized controlled trials are currently investigating the use of HCQ for prophylaxis of COVID-19.[72] Moreover, guidelines from different countries have listed some investigational drugs (including HCQ) as potential adjuvant treatment options, while cautioning to take into account the individual risk of harm.[85,86] Therefore, a careful risk-benefit assessment of HCQ is required for the most cautious use of this drug in subjects with diabetes.

DISCLOSURE
None declared.

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