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PROPOSTA DE ESQUEMA PROFILÁTICO PARA PROFISSIONAIS DE SAÚDE ASSINTOMÁTICOS ENVOLVIDOS NO TRATAMENTO DE CASOS SUSPEITOS, OU CONFIRMADOS, DA COVID-19:

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INTRODUÇÃO

O coronavírus 2 da Síndrome Respiratória Aguda Grave (SARS-CoV-2), vírus responsável pela doença respiratória provocada pelo coronavírus 2019 (COVID-19) é responsável por mais de 964.603 casos positivos e 49.240 mortes em todo o mundo (02 de abril, 14:48 GMT; https://www.worldometers.info/coronavirus/).

Análogos da cloroquina inibem a acidificação dos endossomos e exibem in vitro uma atividade antiviral inespecífica em alta concentração micromolar contra uma ampla gama de vírus emergentes (HIV, dengue, hepatite C, chikungunya, influenza, Ebola, SARS e MERS) e, mais recentemente, COVID-19 (1-2).

Embora não existam medicamentos aprovados pela *Food and Drug Administration* (FDA) ou pela ANVISA (Agência Nacional de Vigilância Sanitária) para prevenir ou tratar o COVID-19, o fármaco hidroxicloroquina, associado à azitromicina, demonstrou inibir o crescimento de SARS-CoV-2 in vitro.

Com o número de casos de COVID-19 e o número de mortes de profissionais de saúde atuando na linha de frente vem aumentando a cada dia que passa, houve a necessidade urgente de utilizar medicamentos com potencial de prevenir infecções por SARS-CoV-2, bem como de atenuar a gravidade das infecções resultantes, o que levou ao uso em circunstâncias especiais (“off label" ou "uso compassivo"), de hidroxicloroquina e azitromicina.

Existe uma forte racionalidade para o uso da cloroquina no tratamento de infecções por microrganismos intracelulares. Assim, a cloroquina e seu análogo hidroxicloroquina são utilizados há quase 80 anos na profilaxia e terapêutica para a malária. Atualmente a hidroxicloroquina é utilizada no tratamento da artrite reumatoide, no lúpus eritematoso sistêmico, sarcoidose, porfiria e na artrite idiopática juvenil. Em 2017, foi o 128º medicamento mais prescrito nos Estados Unidos, com mais de cinco milhões de prescrições.

PROFISSIONAIS DE SAÚDE

Os profissionais de saúde estão na linha de frente no combate à Pandemia de COVID-19 e, como tal, estão expostos a riscos que os colocam em alta probabilidade de infecção. Os riscos incluem exposição a patógenos, longas horas de trabalho, sofrimento psicológico, fadiga, desgaste profissional, estigma e violência psicológica, além de em alguns momentos haver escassez de equipamentos de proteção individual (máscaras, luvas, óculos, aventais,

desinfetante para as mãos, sabão e água, material de limpeza), requisitos fundamentais de segurança e saúde ocupacional.

Os últimos dados da Espanha mostram que aproximadamente 14% dos casos de COVID-19 são de profissionais da saúde. Na Itália, pelo menos 2.629 profissionais foram infectados pelo coronavírus, desde o início da pandemia em fevereiro (report published on Wednesday by Gruppo Italiano per la Medicina Basata sulle Evidenze or GIMBE - Italy's Group for Evidence-based Medicine).

Embora, não disponhamos dos números oficiais de profissionais da saúde que testaram positivo para COVID-19, é do conhecimento geral que centenas deles foram a óbito no exercício de suas funções. Só no Irã 291 óbitos foram registrados até o dia 10 de março de 2020. O número de profissionais de saúde infectados até a presente data (30/03/2020) é de aproximadamente 6,4 mil na Itália, 4 mil na Espanha e 1,7 mil na China. O número de óbitos entre esses profissionais ainda é incerto. Sabe-se que na Itália 51 médicos já faleceram e o número de óbitos entre todos os profissionais da saúde que estão na linha de frete da batalha contra a COVID-19 continua aumentando.

USO PROFILÁTICO DE HIDROXICLOROQINA NA INFECÇÃO POR CORONAVÍRUS

Em 28 de março de 2020 a “Força Nacional de combate à COVID-19” na Índia, constituída pelo Conselho de Pesquisa Médica da Índia (Indian Council for Medical Research) recomendou o uso de hidroxicloroquina como medicação profilática em população de alto risco (profissionais de saúde assintomáticos envolvidos no tratamento de casos suspeitos ou confirmados de doença COVID-19 e contatos domésticos assintomáticos de casos confirmados em laboratórios).

JUSTIFICATIVA PARA USO

HIDROXICLOROQUINA

Possui atividade in vitro contra SARS-CoV-2 e pode ter propriedades imunomoduladoras. Ao nível celular, esses fármacos antimaláricos se acumulam nas vesículas intracelulares, como endossomas e lisossomos, onde são protonados, levando ao aumento do pH vesicular. Por sua vez, isso inibe a atividade das proteases dependentes de pH envolvidas no processamento

intracelular de proteínas secretoras com vários efeitos imunológicos e não imunológicos, incluindo o fator de necrose tumoral α e interleucina 6.

Os mecanismos podem incluir a inibição de enzimas ou processos virais como DNA polimerase e RNA viral, glicosilação de proteínas virais, transporte de partículas de vírus e liberação de vírus. Outros mecanismos também podem envolver ACE2 inibição do receptor celular, acidificação na superfície da membrana celular inibindo fusão do vírus e imunomodulação na liberação de citocinas. Além disso, a cloroquina e a hidroxicloroquina possuem propriedades antivirais in vitro. Acredita-se que a cloroquina e a hidroxicloroquina atuem nos estágios de entrada e pós-infecção da infecção por SARS-CoV e SARS-CoV-2, provavelmente por efeitos no pH endossômico e na subglicosilação resultante dos receptores da enzima conversora de angiotensina 2 (ACE2) que são necessários para a entrada viral. Com base nesses dados in vitro, foi levantada a hipótese de que a hidroxicloroquina, mais do que a cloroquina, pode ter eficácia terapêutica na pandemia de COVID-19 por prevenir a infecção por SARS-CoV-2 inibindo a entrada viral mediada por ACE2 (ou seja, profilaxia da infecção) e também por atenuar a tempestade de citocinas pós-viral observada em casos graves de COVID-19 através de uma multiplicidade de mecanismos imunomoduladores (isto é, tratamento de infecção ativa / e dos efeitos imunes da infecção viral).

ZINCO

Estudos em cultura de células, altas concentrações de Zn^{2+} e a adição de compostos que estimulam o transporte celular de $Zn^{2+,}$ mostraram a inibição da replicação de vários vírus de RNA, incluindo vírus influenza, vírus sincicial respiratório e vários picornavírus, sugerindo que os níveis intracelulares de Zn^{2+} afetam uma etapa comum no ciclo replicativo desses vírus. Para alguns vírus, esse efeito foi atribuído à interferência no processamento da poliproteína viral. Também foi demonstrado que a combinação de Zn^{2+} e PT (pyrithione) em baixas concentrações (2 mM Zn^{2+} + e 2 mM PT) inibe a replicação do SARS-coronavírus (SARS-CoV) e do vírus da arterite equina (EAV) em cultura de células. Em 2010 pesquisadores da Universidade da Carolina do Norte, EUA, mostraram que o Zn^{2+} inibe eficientemente a atividade de síntese de RNA dos RTCs de ambos os vírus. Estudos enzimáticos usando RdRps recombinantes (SARS-CoV nsp12 e EAV nsp9) purificados de *E. coli* revelaram subsequentemente que o Zn^{2+} inibia diretamente a atividade in vitro de ambas as polimerases de nidovírus.

Interferons lambda (IFNL), IFN-λ são citocinas pró-inflamatórias importantes na infecção viral aguda e crônica. Em 2017 pesquisadores da Universidade de Sydney-Austrália evidenciaram que o zinco interfere com a ligação do IFN-3 ao receptor 1 do IFNL (IFNLR1) resultando em diminuição da atividade antiviral

A hidroxicloroquina associada ao zinco pode ter efeitos antivirais contra a SARS-COV2, o que potencialmente pode prevenir a COVID-19.

PROPOSTA DE UM ESQUEMA PROFILÁTICO PARA PROFISSIONAIS DE SAÚDE ASSINTOMÁTICOS ENVOLVIDOS NO TRATAMENTO DE CASOS SUSPEITOS OU CONFIRMADOS DA COVID-19:

HIDROXICLOROQUINA:

400 mg duas vezes, no dia 1 (almoço e jantar).

400 mg uma vez ao dia, no dia 2, 3, 4, e 5 (almoço ou jantar), seguidos por 400 mg uma vez por semana durante as próximas 7 semanas.

ZINCO: 66 miligramas de sulfato de zinco por dia após a refeição (almoço ou Jantar) durante 8 semanas.

CONTRAINDICAÇÕES

Em pessoas com caso conhecido de retinopatia, insuficiência hepática, insuficiência renal, hipersensibilidade conhecida à compostos de 4-aminoquinolina, doenças inflamatórias do cólon, ECG com QT longo ou arritmias.

EFEITOS COLATERAIS

Os efeitos colaterais mais comuns são náuseas e ocasional dor abdominal com diarreia leve, que geralmente melhoram com o tempo.

Os efeitos adversos mais graves afetam o olho, como a retinopatia relacionada à dose como uma preocupação, mesmo após a interrupção do uso da hidroxicloroquina. Tais problemas de visão são mais prováveis de ocorrer em indivíduos que tomam altas doses por muitos anos,

indivíduos com 60 anos ou mais, ou naqueles com doença renal ou hepática significativa. Ressalte-se que a retinopatia pelo uso da hidroxicloroquina é muito rara na dose proposta.

Os efeitos adversos podem incluir: dor de cabeça, tontura, perda de apetite, náusea e vômito, diarreia, dor de estômago/cólicas abdominais e erupção cutânea.

Os efeitos colaterais menos comuns incluem erupção cutânea, alterações no pigmento da pele alterações capilares e fraqueza muscular. Raramente, a hidroxicloroquina pode levar à anemia. Isso pode acontecer em indivíduos com deficiência de G6PD ou porfiria.

SE VOCÊ APRESENTAR ALGUM DOS SEGUINTES SINAIS/SINTOMAS, SUSPENDA O MEDICAMENTO E COMUNIQUE AO MÉDICO RESPONSÁVEL POR SUA PRESCRIÇÃO:

Alterações visuais, sensibilidade à luz, visão a distância embaçada, lampejos ou estrias de luz, dificuldade em ouvir, zumbido, fraqueza ou dor muscular, sangramento ou hematomas na pele, clareamento ou perda de cabelo, alterações no humor ou alterações mentais, arritmias, sonolência, convulsões, tosse e diarreia.

PREOCUPAÇÕES DE SEGURANÇA

Embora os perfis de segurança coletiva da cloroquina e da hidroxicloroquina sejam relativamente favoráveis, ambos os medicamentos bloqueiam o canal de potássio hERG / Kv11.1 codificado por KCNH2 e podem prolongar potencialmente o QTc, com risco de arritmias cardíacas (por exemplo, prolongamento do intervalo QT).

INTERAÇÕES MEDICAMENTOSAS

NÃO É RECOMENDADO o uso de hidroxicloroquina com nenhum dos seguintes medicamentos.

Amisulprida; Aurotioglucose; Bepridil, Cisaprida, Dronedarona, Mesoridazina, Pimozida, Piperaquine, Saquinavir, Sparfloxacina, Terfenadina, Tioridazina, Ziprasidona

O USO DESTE MEDICAMENTO COM QUALQUER UM DOS SEGUINTES MEDICAMENTOS GERALMENTE NÃO É RECOMENDADO, MAS PODE SER NECESSÁRIO EM ALGUNS CASOS. SE OS DOIS MEDICAMENTOS FOREM PRESCRITOS EM CONJUNTO, O SEU

MÉDICO PODE ALTERAR A DOSE OU A FREQUÊNCIA COM QUE VOCÊ USA UM OU AMBOS OS MEDICAMENTOS.

Alfuzosina, Amiodarona, Amitriptilina, Anagrelida, Apomorfina, Aripiprazol, Aripiprazol, Lauroxil, Trióxido de Arsênico, Asenapina, Astemizol, Atazanavir, Auranofin, Azitromicina, Bedaquilina, Buprenorfina, Busserelina, Ceritinibe, Clorpromazina, Ciprofloxacina, Citalopram, Claritromicina, Clofazimina, Clomipramina, Clozapina, Crizotinibe, Ciclobenzaprina, Dabrafenibe, Dasatinibe, Degarelix, Delamanida, Desipramina, Deslorelina, Deutetrabenazina, Disopiramida, Dofetilida, Dolasetrona, Domperidona, Donepezil, Doxepina, Droperidibidina, Familidina, Efastina Felbamato, Fingolimode, Flecainida, Fluconazol, Fluoxetina, Formoterol, Foscarnet, Fosfenitoína, Galantamina, Gatifloxacina, Gemifloxacina, Glasdegib, Gonadorelina, Goserelina, Granisetrona, Halofantrina, Haloperidol, Hoperelina, Histrelin, Hidroxiquinina, Hidroxizinina, Ibutilide, Iloperidona, Imipramina, Inotuzumab Ozogamicina, Itraconazol, Ivabradine, Ivosidenib, Ketoconazole, Lapatinibe, Lefamulin, Lenvatinib, Leuprolide, Levofloxacina, Lofexidine, Lumefantrine, Macimorelin, Mefloquine, Metadona, Metotrimeprazina, Metronidazole, Mifepristone, Mizolastine, Moricizine, Moxprolacina, Noxiflacina, Octreotide, Ofloxacina, Olanzapina, Ondansetrona, Osimertinibe, Paliperidona, Panobinostat, Paroxetina, Pasireotida, Pazopanibe, Pentamidina, Perfenazina, Pimavanserina, Pipamperona, Pitolisant, Posaconazol, Probucol, Procainamida, Proclorperazina, Prometazina, Propafenona, Protriptilina, Quetiapina, Quinidina, Quinino, Ranozalina, Ribociclib, Rilpivirine, Risperidona, Ritonavir, Sertindol, Sertralina, Sevoflurano, Siponimod, Fosfato de sódio, Fosfato de sódio dibásico, Fosfato de sódio monobásico, Solifenacina, Sorafenibe, Sotalol, Sulpirida, Sultoprida, Sunitinibe, Tacrolimus, Tamoxifeno, Telaprevir, Telavancina, Telitromicina, Tetrabenazina, Tizanidina, Tolterodina, Toremifene, Toroxifina, Toxifenidina, Trazodona, Triclabendazol, Trimipramina, Triptorelina, Vandetanibe, Vardenafila, Vemurafenibe, Venlafaxina, Vilanterol, Vinflunina, Voriconazol, Vorinostat, Zotepina, Zuclopentixol.

OUTRAS INTERAÇÕES

O uso de álcool ou tabaco com certos medicamentos também pode causar interações. Discuta com seu médico o uso de seu medicamento com alimentos, álcool ou tabaco.

OUTROS PROBLEMAS MÉDICOS -

A presença de outros problemas médicos pode afetar o uso deste medicamento. Informe o seu médico se tiver outros problemas médicos, especialmente:

Alergia a compostos de 4-aminoquinolina (por exemplo, cloroquina) - não deve ser usado nessa condição.

Diabetes, Problemas oculares ou visuais, Problemas musculares, Problemas nervosos, Porfiria, Psoríase, Doenças do trato gastrintestinal, Deficiência de glicose-6-fosfato desidrogenase (G6PD) (risco de anemia hemolítica), Doença renal ou hepática (uso com cautela). Os efeitos podem ser aumentados devido à diminuição da eliminação/clearance.

FARMACOCINÉTICA – FARMACODINÂMICA DA HIDROXICLOROQUINA

A hidroxicloroquina possui farmacocinética semelhante à cloroquina, com rápida absorção e eliminação gastrointestinal e pelos rins. As enzimas do citocromo P450 (CYP2D6, 2C8, 3A4 e 3A5) metabolizam a hidroxicloroquina em N-desetil-hidroxicloroquina.

Após dose oral única de 200 mg em voluntários saudáveis, a concentração média máxima de hidroxicloroquina no sangue foi de 129,6 ng / mL, com Tmax de 3,26 horas, e meia-vida de 537 horas (22,4 dias). Os parâmetros farmacocinéticos não foram significativamente diferentes no intervalo de doses terapêuticas de 155 mg e 310 mg, indicando cinética linear.

Após administração oral crônica de hidroxicloroquina, foram encontrados níveis significativos dos metabólitos desetil-hidroxicloroquina (DHCQ), desetilcloroquina (DCQ) e bidesetil-hidroxicloroquina (BDCQ) no plasma e no sangue, sendo o DHCQ o metabólito principal. A meia-vida de absorção foi de aproximadamente 3 a 4 horas e a meia-vida terminal variou de 40 a 50 dias. A meia-vida longa pode ser atribuída à captação extensiva de tecidos, e não pela diminuição da excreção. Os níveis plasmáticos máximos de hidroxicloroquina foram observados em cerca de 3 a 4 horas.

RECOMENDAÇÕES IMPORTANTES

É importante ressaltar que os profissionais de saúde sob quimioprofilaxia não devem negligenciar as normas de segurança. Devem continuar seguindo todas as medidas de saúde

pública prescritas, como lavar as mãos com frequência, seguir as recomendações de proteção respiratórias (proteção para tosses, espirros), manter distância mínima de 1m e usar equipamento de proteção individual adequados (quando trabalhando).

Os profissionais de saúde devem auto monitorar sua saúde e reportar-se imediatamente às autoridades, caso apresentem sintomas de síndrome gripal ou relacionados ao COVID-19.

Os contatos de alto risco de um caso positivo de COVID-19 de profissional de saúde colocado sob quimioprofilaxia devem permanecer em quarentena e serem monitorados de perto.

O medicamento deve ser administrado apenas sob a prescrição de um médico. As contraindicações mencionadas nas recomendações devem ser rigorosamente seguidas.

Se o profissional de saúde em quimioprofilaxia desenvolver outros sintomas, que não os de uma síndrome gripal ou relacionados com o COVID-19, deve procurar imediatamente aconselhamento médico.

CONCLUSÕES

Não existe medicamento sem efeitos colaterais, entretanto a hidroxicloroquina tem se mostrado segura quando utilizada nas doses recomendadas e por tempo reduzido (menos de três meses). Em medicina as decisões são tomadas sempre avaliando o binômio risco/benefício. Como essa pandemia provocada pelo coronavírus continua a se disseminar dizimando milhares de vidas, incluindo profissionais de saúde, achamos importante utilizar os nossos conhecimentos para sugerir uma terapêutica profilática com um medicamento relativamente seguro, para os profissionais de saúde que se encontram na linha de frente do combate a SARS-CoV-2.

Embora, não exista nenhum ensaio clínico publicado sobre a profilaxia da COVID-19 usando hidroxicloroquina, o esquema proposto está baseado no mesmo princípio de prevenção da Malária quando o indivíduo se desloca para uma área endêmica. Foi alicerçada também na determinação do *Indian Council for Medical Research* que está fazendo o uso profilático da hidroxicloroquina para os profissionais de saúde e também para os contatos familiares assintomáticos. Além disso, pode-se justificar o seu uso profilático como uma “terapia de Salvamento Experimental” considerando o elevado número de profissionais que já contraíram a COVID-19 em todo o mundo, da mesma forma como está sendo proposto o uso da hidroxicloroquina para os pacientes com sintomatologia leve, moderada e grave com a mesma

doença. Seria o mesmo que realizar um estudo Fase II: um tipo específico de voluntários (profissionais da saúde) com uma terapia profilática exposto à uma doença.

A associação com zinco está fundamentada na literatura pela sua atividade em diversas doenças virais, especialmente nas crianças.

Sugerimos realizar também, antes de iniciar a profilaxia com Hidroxicloroquina e sulfato de zinco, para maior segurança:

- Um eletrocardiograma basal e outro após 72h.

- Avaliar parâmetros bioquímicos (incluindo cálcio, potássio, magnésio, zinco e cobre);

- Avaliar parâmetros hematológicos.

Esperamos que uma ampla adoção e utilização deste esquema terapêutico possa reduzir o número de infectados e, consequentemente, o número de mortes entre os profissionais de saúde. Entretanto, é importante ressaltar que, como ainda não existem evidências que comprovem a eficiência desta proposta, as medidas preventivas de contaminação, como o uso de EPIs, não devem ser negligenciadas.

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Advisory on the use of hydroxy–chloroquine as prophylaxis for SARS-CoV-2 infection

The **National Task force for COVID-19** constituted by Indian Council of Medical Research recommends the use of hydroxy– chloroquine for prophylaxis of SARS-CoV-2 infection for high risk population. Copy is annexed.

The Advisory provides for placing the following high risk population under chemoprophylaxis with hydroxy chloroquine:

- Asymptomatic Healthcare Workers involved in the care of suspected or confirmed cases of COVID-19
- Asymptomatic household contacts of laboratory confirmed cases

The protocol recommended by the National Task force has been approved by the Drug Controller General of India for restricted use in emergency situations.

While following the above recommendations, States should take note of the following:

1) **The placing of healthcare workers under chemoprophylaxis should not instill a sense of false security.** They should follow all prescribed public health measures such as frequent washing of hands, respiratory etiquettes, keeping a distance of minimum 1m and use of Personal protective equipment (wherever applicable).
2) They should self-monitor their health and report to health authorities immediately in the event of them becoming symptomatic.
3) The high risk contacts of a positive case placed under chemo prophylaxis, **should remain in home quarantine while on prophylactic therapy.**
4) As recommended by the said Task Force, the drug should only be given on the prescription of a registered medical practitioner. The contraindications mentioned in the recommendations should strictly be followed.
5) Apart from the symptoms of COVID-19 (fever, cough, breathing difficulty), if the person on chemo-prophylaxis develops any other symptoms, he should immediately seek medical treatment of the medical practitioner who has prescribed the chemoprophylaxis.

It is reiterated that the intake of the above medicine should not in still sense of false security.

ANNEXURE I

सत्यमेव जयते

प्रोफेसर (डा.) बलराम भार्गव, पदम श्री

एमडी, डीएम, एफआरसीपी (जी.), एफआरसीपी (ई.), एफएसीसी, एफएएचए, एफएएमएस, एफएनएएस, एफएएसी, एफ.एन.ए., डी.एस.सी.

सचिव, भारत सरकार

स्वास्थ्य अनुसंधान विभाग

स्वास्थ्य एवं परिवार कल्याण मंत्रालय एवं

महानिदेशक, आई सी एम आर

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भारतीय आयुर्विज्ञान अनुसंधान परिषद

स्वास्थ्य अनुसंधान विभाग

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New Delhi - 110 029

D.O.No.VIR/4/2020/ECD-I

22nd March, 2020

Dear Madam

Please find attached the final recommendation of the National Taskforce for COVID-19 for the use of hydroxychloroquine as prophylaxis. This recommendation supersedes the earlier recommendation dated 21.3.2020

With regards

Yours sincerely,

Balram Bhargava

(Balram Bhargava)

Encl: As above

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Recommendation for empiric use of hydroxy-chloroquine for prophylaxis of SARS-CoV-2 infection

Background:

Hydroxy-chloroquine is found to be effective against coronavirus in laboratory studies and in-vivo studies. Its use in prophylaxis is derived from available evidence of benefit as treatment and supported by pre-clinical data. The following recommendation for the use of hydroxy-chloroquine as a prophylactic agent against SARS-CoV-2 infection is based on these considerations, as well as risk-benefit consideration, under exceptional circumstances that call for the protection of high-risk individuals.

The National Taskforce for COVID-19 recommends the use of hydroxy-chloroquine for prophylaxis of SARS-CoV-2 infection for selected individuals as follows:

Eligible Individuals:

- Asymptomatic healthcare workers involved in the care of suspected or confirmed cases of COVID-19
- Asymptomatic household contacts of laboratory confirmed cases

Dose:

- Asymptomatic healthcare workers involved in the care of suspected or confirmed cases of COVID-19: *400 mg twice a day on Day 1, followed by 400 mg once weekly for next 7 weeks; to be taken with meals*
- Asymptomatic household contacts of laboratory confirmed cases: *400 mg twice a day on Day 1, followed by 400 mg once weekly for next 3 weeks; to be taken with meals*

Exclusion/contraindications:

- The drug is not recommended for prophylaxis in children under 15 years of age.
- The drug is contraindicated in persons with known case of retinopathy, known hypersensitivity to hydroxychloroquine, 4-aminoquinoline compounds

Key considerations:

- The drug has to be given only on the prescription of a registered medical practitioner.
- Advised to consult with a physician for any adverse event or potential drug interaction before initiation of medication
- The prophylactic use of hydroxychloroquine to be coupled with the pharmacovigilance for adverse drug reactions through self-reporting using the Pharmacovigilance Program of India (PvPI) helpline/app.
- If anyone becomes symptomatic while on prophylaxis he/she should immediately contact the health facility, get tested as per national guidelines and follow the standard treatment protocol.
- All asymptomatic contacts of laboratory confirmed cases should remain in home quarantine as per the national guidelines, even if they are on prophylactic therapy.
- Simultaneously, proof of concept and pharmacokinetics studies be taken up expeditiously. Findings from these studies and other new evidence will guide any change in the recommendation.

Improving the efficacy of chloroquine and hydroxychloroquine against SARS-CoV-2 may require zinc additives - A better synergy for future COVID-19 clinical trials

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SUMMARY

The recent outbreak of coronavirus disease 2019 (COVID-19), has now been officially declared as a pandemic by the World Health Organization. As of now, there is no known effective pharmaceutical agent against the SARS-CoV-2 virus. However, several precautionary measures have been prescribed to prevent further spread of the virus, which include avoidance of social gatherings, proper handwashing, frequently disinfecting of used items and surfaces and so on. More recent studies have highlighted the possibility of treating patients infected with the novel SARS-CoV-2 virus with chloroquine and hydroxychloroquine, of which mechanism of action is not completely understood. We seek to draw the attention of the scientific community to the possibility of drastically reducing the effects of the virus on the affected patients and improving clinical trials outcome through the synergistic action of zinc and chloroquine in patients suffering from the coronavirus disease.

Keywords: coronavirus, COVID-19, chloroquine, hydroxychloroquine, zinc, SARS-CoV-2.

INTRODUCTION

The coronavirus disease named COVID-19 by the World Health Organization, which originated from Wuhan, the capital city of Hubei province in China in December 2019 has sporadically spread throughout the world. As of today, the 16th of April 2020, over 2 million cases and 134,000 deaths have been reported in 210 countries and territories around the world [1]. The total number of cases in the United States, Spain, Italy, Germany, and France have surpassed the cases in China where the infection was originally discovered. Currently, comparative genomics studies have been deployed by some countries in Europe and North America to trace the origin of SARS-CoV-2 and to understand its evolution for proper monitoring of multiple aspects of this pandemic [2]. The infection is currently constituting a serious health, economic, social, and psychological effects on the whole world as the world is under lock down as a measure to curb the spread of the virus.

Coronaviruses (CoVs) belong to the family of *Coronaviridae*. They have a non-segmented, single-stranded, positive-sense RNA genome [3]. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes COVID-19 is a zoonotic pathogen, which can infect both human and animal. This virus is believed to have crossed the species barrier to infect humans [3]. It has been

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suggested that human contract the SARS-CoV-2 through close contact with the animals, but there is also the possibility of foodborne transmission [4]. COVID-19 is thought to spread from person to person through respiratory droplets produced when an infected person coughs or sneezes within a proximity to an uninfected person, usually within 6 feet. Another way of spreading the virus is by touching your mouth, nose, or eyes after touching a surface or object that has the virus.

This virus infects the host cell through a non-pH dependent endocytosis by attaching to the type I integral membrane receptor angiotensin-converting enzyme-2 (ACE2) in the alveolar cells in the lungs with its glycoproteins [5]. Patients affected with SARS-CoV-2 may progress from the asymptomatic state to Acute Respiratory Distress Syndrome (ARDS) and septic shock in severe form of the disease. The common clinical features of COVID-19 include cough, sore throat, fatigue, headache, myalgia, dyspnea, and fever (not in all cases) [6].

Currently, there is no proven treatment for COVID-19 infection. However, there is a growing evidence that chloroquine and hydroxychloroquine broadly used as antimalarial and immunomodulatory drugs can be used in the treatment of patients with COVID-19 infection. Chloroquine and hydroxychloroquine belong to the same molecular family. The difference between the two is the presence of hydroxyl group at the end of the side chain of hydroxychloroquine. They are both active against malaria parasite, but hydroxychloroquine is less toxic [7]. Several *in vitro* studies and recent clinical trials have shown the efficacy of chloroquine in patients with COVID-19 at different levels of severity [8-10]. In a recent report, chloroquine was cited as a potential remedy to alleviate exacerbation of pneumonia and mitigate inflammatory response, which improves the disease outcome [9]. This is not the first-time chloroquine and hydroxychloroquine are being used to treat a novel emerged virus, there are evidences for the activities of chloroquine and hydroxychloroquine against Zika virus, Ebola virus, and Chikungunya virus [11-13]. Nevertheless, the mechanism of action of chloroquine on COVID-19 is not yet fully understood. However, several putative mechanisms describing the effects of chloroquine on the replication cycle of SARS-CoV-2 have been reported [7, 14].

Zinc is another substance that could reduce the SARS-CoV-2 viral activities when consumed due to its antiviral effect and perhaps alleviate the respiratory tract infection. Zinc is the second most abundant trace element, which exists in the divalent cation state in the body. Only a little free zinc exists because it readily binds to protein to form a metalloprotein. The primary source of zinc is a diet rich in fish, eggs, dairy products, shellfish (especially oysters), and red meat. In human, zinc supplementation is the key to constant supply of zinc and maintaining homeostasis as the ability of the body to store zinc is limited [15]. Zinc plays important roles in immunity and viral infection. Replication of SARS-coronavirus, hepatitis C virus, H1N1 influenza virus has been shown to be inhibited by zinc oxide and zinc salt. How zinc exhibits its antiviral activities is not clearly understood, however, among the possible means is the inhibition of viral binding to the mucosa, suppression of inflammatory effect, generation of antiviral interferon and inhibition of important enzyme in viral replication [16]. Recently, a study conducted by Kaushik et al. unraveled the ability of zinc salts in inhibiting Hepatitis E virus replication through the inhibition of RNA-dependent-RNA-polymerase (RdRp) [17]. Interestingly, this enzyme also plays a key role in coronavirus replication. Therefore, in this article, we will be reviewing the interaction between chloroquine, hydroxychloroquine, and zinc, and the possibility of their synergistic administration to mitigate the exacerbation of COVID-19.

Metal ionophores: their mechanistic interaction with viral replication and disease progression

Accumulated evidences in past studies have revealed that metal ionophores are drug compounds that have metal-binding domains which enable them to act as transporters of cations such as Ca^{2+}, Zn^{2+}, Na^{+} and Cu^{2+} [18-20]. Metal ions act as ligands that catalyze many downstream roles which promotes many key cellular processes. Deficiencies in concentration of metal ions like zinc, calcium or iron will significantly alter cellular signal transduction, DNA synthesis and mRNA transcription, protein aggregation and protein function [21, 22]. The ability of metal ionophores to reduce metal ion availability in extracellular matrix (ECM) of living tissues allow them to move excess ions into the cytosol thereby

affecting signal transduction [18, 23]. Drug compounds such as clioquinol, pyrithione (PT), hydroxyquinoline, chloroquine (CQ) and hydroxychloroquine (CQ) have been described as metal ionophores which can transport ion ligands that drive down stream cell signaling processes from the ECM into the cell in large amounts [23, 24]. Clioquinol and hydroxyquinoline can bind and transport Zn^{2+} and Cu^{2+} ions into cancer cells that express excess glucose receptors, causing severe metal ion toxicities and triggering the apoptotic program [25]. Similarly, metal ionophores act as weak bases and can bind excess zinc salts in viral transfected tissues and then directly interfere in synthesis of viral DNA dependent DNA polymerase or RNA dependent RNA polymerase [26]. Conversely, certain metal ionophores such as clioquinol can increase the levels of intracellular zinc in the lysosomes of cancer cells leading to lysosome-mediated apoptosis [21].

Metal ionophores may also act as chelators; a clinical trial investigation showed that drug compounds such as desferrioxamine and tetrathiomolybdate suppressed tumor clonal expansion, metastases and angiogenesis [19]. Meanwhile, clioquinol (5-chloro-7-iodo-8-hydroxyquinoline) can inactivate superoxide dismutase-1 (SOD1) and precipitate halt in cancer progression [25]. Similarly, Daniel et al., showed that dithiocarbamate requires zinc metal ions to inhibit NF-kappa B [27]. They study also showed that zinc ions are need for PT to cause a 10-fold potency for inhibition of NF-kappa B. The zinc ionophore PT (1-hydroxypyridine-2-thionine) has been described to have antiviral properties and has been proven a potent industrial biocide [27]. In 2009, Ding and Lund reported that with adequate zinc additives, PT when added to cells along with induced apoptosis and that a zinc additive-PT treatment of viral transfected cells can represent a good frontier for clinical trial of antiviral drugs [21]. Furthermore, a later study demonstrated that novel fluorinated 8-hydroxyquinoline based metal ionophore showed potency for amyloid-beta (Aβ) deposition and stabilization in Alzheimer's disease (AD) [20]. Summarily, metal ionophores have been proven over the years to exert overt antiviral and anticancer properties especially when coupled with enough doses of metal ion additives that will galvanize their functions in living tissues.

Chloroquine and hydroxychloroquine as zinc ionophores: indirect interaction with COVID-19 genome replication

Chloroquine (CQ) is a 4-aminoquinoline antimalaria drug that has also been used over the years as an anti-inflammatory agent and as an anticancer drug [28, 29]. CQ and its derivative hydroxychloroquine (HCQ) act as weak bases that can target key cellular signal transduction organelles such as lysosomes and Golgi [30, 31]. An accumulated concentration of CQ in these organelles will catalyze significant disruption of downstream signaling processes via increase in the endosomal and lysosomal pH [28, 31]. Although, continuous study on the putative mechanism of action of CQ are still ongoing in molecular medicine, however, past studies showed that upon administration, the bioavailability of CQ and HCQ hinges largely upon their protonation with zinc ions (Zn^{2+}) upon the cell, which makes them have high affinity for low-pH organelles [32, 33]. By catalyzing an increase in the pH, CQ and HCQ impair maturation of cell lysosomes and autophagosomes, thereby inhibiting antigen presentation tendency of the host cell [31, 34]. This direct interference with lysosomal activity upon inhibition triggers an immunostimulatory response against the host cell via MHC class II presentation [33, 34]. Xue et al. showed that CQ and HCQ are zinc ionophores using human ovarian cancer cell line (A2780) [33]. They reported that at dose dependent concentrations, CQ and HCQ enhanced Zn^{2+} uptake by TPEN attenuated A2780 cells in a concentration-dependent manner. Furthermore, microscopic probe of intracellular zinc distribution demonstrated that consistent with previous studies, CQ and HCQ delivered free Zn^{2+} ions to the lysosomes inhibiting lysosomal function. The same study also suggested that a combination of CQ or HCQ with zinc enhanced chloroquine's cytotoxicity and induced apoptosis in A2780 cells [33].

Meanwhile, a study by te Velthuis et al. links an increase in the intracellular Zn^{2+} ion concentration by PT with replication impairments in RNA dependent RNA polymerase viruses such as poliovirus and influenza virus [35]. In the same study, the potency of PT zinc ionophore against these viruses was attributed to interference with polyprotein processing of RNA viruses. Meanwhile the same study also demonstrated that a combination of PT zinc ionophore with Zn^{2+} ions inhibited the

replication of RNA dependent RNA polymerase viruses; SARS-coronavirus (SARS-CoV) and equine arteritis virus (EAV) in cell culture. The RNA-dependent RNA polymerase (RdRp) is a core enzyme of RNA viruses that enable multiprotein replication and transcription complex (RTC) formation [35]. The same study by te Velthuis et al. used an activity assay procedure to show that without Zn^{2+}, PT was unable to effectively hinder (90%) the RNA-synthesizing activity of the RTCs of both SARS-CoV or EAV viruses [35]. They also reported further that enzymatic studies using recombinant RdRps of SARS-CoV nsp12 and EAV nsp9 showed that PT was only a transporter and that Zn^{2+} directly inhibited the activity of their polymerases *in vitro*. Hence, while PT was an ionophore that carried Zn^{2+} into the cell, Zn^{2+} acted to block the initiation of EAV RNA synthesis and SARS-CoV RdRp elongation was inhibited so that RNA template binding was reduced. Conversely, another study by Kaushik et al. investigated the effect of zinc salts on RNA replication of hepatitis E virus (HEV) using hepatoma cell (Huh7) cultures [17]. It was reported that zinc salts transported by PT inhibited the RNA replication of g-3 HEV replicons and g-1 HEV infectious genomic RNA in a dose-dependent manner [17]. Analysis of a replication-defective mutant of g-1 HEV genomic RNA showed that zinc salts directly inhibit the activity of viral RdRp, leading to inhibition of viral replication [17]. In summary, zinc ionophores such as CQ, PT and HCQ have demonstrated promising prospects for successful clinical trials by *in vivo* and *in vitro* studies where their administration is coupled with zinc supplements.

Combining CQ and HCQ use with zinc supplements: synergism needed for successful COVID-19 clinical trials?

A variety of compelling evidences have been published from early clinical trials in China that showed the efficacy of CQ and HCQ in the treatment of SARS-CoV-2. The long trail of studies showed the possibility that CQ and its derivatives may be effective against the novel SARS-CoV-2 (the pathogen that causes COVID-19 and shares a close phylogeny with previous species of coronavirus) [8, 10, 36, 37]. A common consensus amongst the published clinical trials was that the SARS-CoV-2 virus requires acidification of endosomes and that essential modifications to its capsid envelope glycoproteins are needed for viral replication which occurs within the endoplasmic and trans-Golgi network vesicles at a low pH in presence of proteases and glycosyl-transferases [8, 37-39]. However, this essential prerequisite for SARS-CoV-2 replication is blocked by CQ and HCQ since the drugs alter ACE2 glycosylation by stopping S-protein binding, thereby interfering with viral replication the cell cytoplasm [9].

Meanwhile, another recent systematic review on the state of CQ and HCQ clinical trials for COVID-19 used PubMed and EMBASE databases from inception to 1-March-2020 to find information on the efficacy and safety of CQ/HCQ formulations in patients diagnosed with SARS-CoV-2 [40]. Their initial search identified 234 sources (156 from PubMed, 73 EMBASE and 5 from other verified sources) amongst which twenty-three clinical trials were found in the trial registries. However, in all these documented clinical trials in Europe and China, the pattern of administration was similar as CQ and HCQ drugs were used without being combined with zinc ion supplements. Incidentally, none of these clinical trials conducted so far has given a near total positive outcome, which is significant enough to trigger an endorsement on a global scale. Perhaps, consistent with previous studies that delineated the efficacy of HCQ and CQ as zinc ionophores, it was rather surprising that none of these clinical trials so far considered using a combination of dose depended zinc supplements with HCQ and CQ administration.

CONCLUSION

Chloroquine can induce the uptake of zinc into the cytosol of the cell, which is capable of inhibiting RNA-dependent RNA polymerase and ultimately halting the replication of coronavirus in the host cell. Currently, there are several clinical trials that are currently underway in several countries of the world to assess the efficacy of chloroquine as an anti-coronavirus agent. Since chloroquine has been widely prescribed for use as an anti-malarial, its safety is not in doubt. In view of the foregoing, clinical trials predicated upon a synergistic administration of Zn supplement with CQ or HCQ against the novel SARS-CoV-2 virus should be considered so that better COVID-19 clinical trial outcomes can be obtained going forward.

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None declared

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Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Cardiovascular risks of hydroxychloroquine in treatment and prophylaxis of COVID-19 patients: A scientific statement from the Indian Heart Rhythm Society

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This statement from Indian Heart Rhythm Society (IHRS) addresses specifically the drug hydroxychloroquine (HCQ) mentioned in these guidelines. This includes a brief review of its cardiovascular effects, with respect to its propensity to cause QT interval prolongation and potentially lethal cardiac arrhythmia in certain patients. Identification of high-risk population and monitoring for prevention of such adverse events of sudden cardiac death are also discussed.

Coronavirus disease 2019 (COVID-19) is now a pandemic as recognized by the World Health Organization (WHO) on March 11, 2020. The disease is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2/2019-nCoV). At the time of release of this statement, as per the available global statistics, more than 1.5 million had infection and around 87000 had died [1]. The corresponding figures in India are 4714 and 149 respectively [2]. There is a distinct possibility of COVID-19 overwhelming the healthcare capacity of India. The measures to contain the spread of COVID-19 such as social-distancing, hand hygiene, surveillance, and isolation of persons suspected or confirmed to have infection have been considered to be largely effective. In this regard, Government authorities have issued guidelines to health care workers and to the public at large, uniformly advising strict adherence to above measures and acknowledge the limited role of drugs in the treatment and prophylaxis of COVID-19 infection.

1. Cardiovascular effects of hydroxychloroquine

The drug, HCQ, is a 4-amino-quinoline that is widely used to treat certain autoimmune disorders, and related inflammatory and dermatological conditions. It is a hydroxylated version of chloroquine – an antimalarial that has been in use for decades, with a similar mechanism of action. HCQ is considered to be safer than chloroquine based on clinical studies [3,4]. This drug has now found place in management of COVID-19 infection [3–10]. It has been observed to inhibit ACE2 receptor-mediated entry of the SARS-CoV2 virus through various actions such as raising of intravesicular pH, inhibiting lysosomal activity, affecting antigen processing, etc. [3–7]. In addition, it has anti-inflammatory and immunomodulator actions which could be relevant in the crisis

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generated by cytokines storm during COVID-19 infection [8–10].

HCQ can lead to QT interval prolongation and torsades de pointes (TdP) in susceptible individuals. The risk of TdP is not a linear function of basal QTc or drug-induced prolongation in QTc interval. Moreover, not all patients with drug-induced QTc prolongation will develop TdP. This side effect is rare, but co-prescription of other drugs such as azithromycin (which is also being recommended for the treatment of COVID-19) could amplify this risk. Many other drugs such as quinolones, antihistamines etc. which are often used may also add to the risk of TdP (refer to https://www.crediblemeds.org/drugsearch for list of drugs associated with QT prolongation). HCQ also interacts with other cardiac drugs such as beta blockers and digoxin and increases the blood levels of these drugs.

2. Recording ECG to measure QTc interval

It is recommended to have a baseline ECG to estimate the QTc interval in individuals receiving HCQ treatment. The QTc interval is calculated by measuring the QT interval on 12-lead ECG and using Bazett's formula. The normal upper limit for QTc interval is 460 ms for women and 450 ms for men [11].

In a situation where 12-lead ECG is not available, one can simply measure the QT interval on a rhythm strip and compare it with RR interval. As a simple 'rule of thumb' QT interval should be less than half of RR interval. In case of doubt or borderline situation, perform a 12-lead ECG and calculate QTc interval. One can also use smartphone app, or an online calculator https://www.qtcalculator.org for calculating QTc interval.

In patients with wide QRS due to underlying intraventricular conduction defects or paced rhythm, use the following formula to estimate QTc interval: wide QRS adjusted QTc = QTc − (QRS duration−100 ms) [11].

3. Alternatives to standard 12-lead ECG in current COVID-19 pandemic

While an ECG is a relatively simple screening tool, it still poses challenges in the current pandemic as screening people by performing multiple ECGs in COVID-19 positive patients is associated with need of personal protective equipment, the risk of contamination of equipment as well as risk to healthcare workers. Accurate measurement also demands a specialist physician's expertise adding further burden on the strained resources. The alternative approaches in these settings could be the following.

1. Standard telemetry systems which are also equipped with real time QTc monitoring is an option. This is especially true for sick, hospitalized COVID-19 patients who may be on continuous rhythm monitoring. The presence of associated dyselectrolytemia, which can further increase the risk of QTc prolongation in these sick patients, makes telemetry a good alternative to 12-lead ECG for this subset.
2. Using a smartphone-enabled mobile QTc app or the FDA-approved mobile ECG devicesuch as AliveCor (Kardia Mobile-6L device), if available, obviates the need of personnel resources to obtain an ECG. The AliveCor was granted emergency approval by the US FDA on March 20, 2020 for this purpose and is currently available in India. If a smartphone or AliveCor app is used, the QTc could be recorded every 12 h.

4. Patients at high risk of hydroxychloroquine-induced QT prolongation and TdP

When HCQ administration is considered for a COVID-19 patient or suspect, efforts should be made to identify all potentially high-risk individuals who should have a baseline ECG recording. In general, ECG is recommended for measurement of QTc interval in all hospitalized COVID-19 patients, before starting HCQ.

Patients can be categorized into a low-risk group with a normal QTc interval (group A), a moderate-risk group with slightly prolonged (up to 500 ms; group B) and a high-risk group with a prolonged QTc interval ≥500 ms (group C) (see Fig. 1).

Besides prolonged QTc interval, certain clinical factors which predispose a person to HCQ toxicity should be noted (Table 1).

5. Recommendations for use of hydroxychloroquine in COVID-19 therapy

The Government of India, Ministry of Health and Family Welfare Guidelines on Clinical Management of COVID-19 (dated March 31, 2020) [12], recommend that following drugs may be considered as an off–label indication in patients with severe disease and

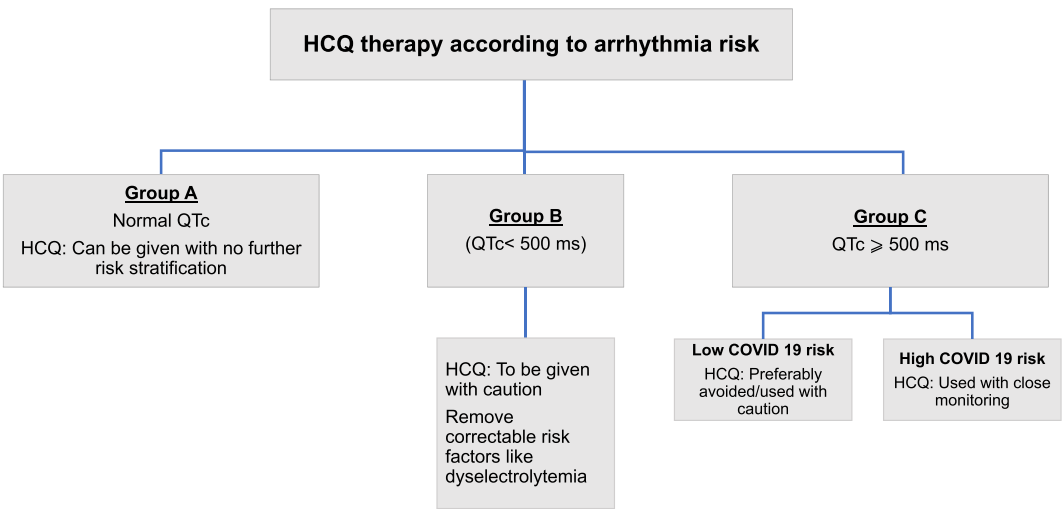

Fig. 1. Hydroxychloroquine therapy according to cardiovascular risk.
Abbreviations: HCQ – Hydroxychloroquine, QTc-corrected QT interval.

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Table 1
Risk factors for hydroxychloroquine-induced arrhythmia.

1. Structural heart diseases especially ventricular hypertrophy or left ventricular dysfunction
2. Previous history of ventricular arrhythmia or syncope
3. History of implantable heart rhythm devices
4. Co-administration of other QT prolonging drugs (macrolides, quinolones, anti-histaminics, antiviral, anti-arrhythmic, or anti-fungal drugs, etc.). (Refer https://crediblemeds.org/pdftemp/pdf/CombinedList.pdf for a detailed list)

requiring ICU management:

- HCQ: 400 mg BD for one day followed by 200 mg BD for 4 days, in combination with
- Azithromycin: 500 mg OD for 5 days.

These drugs should be administered under close medical supervision, with monitoring for side effects including QTc interval. The above regimen is presently not recommended for children less than 12 years, and pregnant or lactating women. These guidelines are based on currently available information (uncontrolled clinical trials) and will be reviewed as new evidence emerges.

5.1. Recommendations for hydroxychloroquine therapy according to arrhythmic risk

a) Those with normal QTc interval (Group A): HCQ can be administered without further risk stratification.
b) Those with slightly prolonged QTc interval (<500 ms; Group B): HCQ should be used with caution with attempts to resolve correctable risk factors.
c) Those with baseline QTc ≥500 ms (Group C): These patients should have clinical evaluation as per Table 1, and can be further subdivided into two categories on basis of COVID-19 risk.
   - Low COVID-19 risk: In patients having lower risk of COVID-19 complications, HCQ should preferably be avoided or used with caution.
   - High COVID-19 risk: In patients having higher risk of COVID-19 complications, HCQ may be used with close monitoring.

5.2. Frequency of ECG monitoring

1. In patients with QTc ≥500 ms at baseline, it is recommended to perform an ECG at 2–4 h after the first dose to measure any change in QTc, and then at 48 and 96 h [13].
2. If there is prolongation in QTc interval by more than 60 ms from baseline, reassess benefit versus risk of continuing HCQ therapy.

6. Recommendations for use of hydroxychloroquine in COVID-19 prophylaxis

The National Task Force for COVID-19 constituted by Indian Council of Medical Research (ICMR) on March 22, 2020 recommended HCQ for prophylactic use [14]. The recommended dosage is as follows.

1. Asymptomatic healthcare workers involved in the care of suspected or confirmed cases of COVID-19: 400 mg twice a day on Day 1, followed by 400 mg once weekly for next 7 weeks, to be taken with meals
2. Asymptomatic household contacts of laboratory confirmed cases: 400 mg twice a day on Day 1, followed by 400 mg once weekly for next 3 weeks; to be taken with meals.

The drug is not recommended for prophylaxis in children under 15 years of age. In addition, the drug is contraindicated in persons with retinopathy, known hypersensitivity to HCQ and 4-aminoquinoline compounds, and pregnant patients.

These recommendations, according to the task force, are based on the evidence of benefit supported by pre-clinical data and under 'exceptional' circumstances. The prophylactic use of HCQ should be coupled with pharmacovigilance for adverse events through self-reporting using the Pharmacovigilance Program of India (PvPI) helpline/App.

When HCQ is used for prophylaxis, although it is preferable to have a baseline ECG to measure the QTc interval, it may not be logistically possible in everyone. However, efforts should be made to identify all potentially high-risk individuals (Table 1) and they should undergo ECG monitoring for QTc interval.

7. Conclusions

Hydroxychloroquine is being used globally for treatment and prophylaxis of COVID-19. Various countries have issued recommendations on its use based on in-vitro, or small clinical studies. In absence of randomized trial data, these recommendations reflect the extraordinary situation of a rapidly evolving pandemic of a highly contagious disease. The guidelines are likely to change as more data from randomized clinical trials is available. The decision to use HCQ for COVID-19 should take into account the occasional possibility of cardiac arrhythmia.

Indian Heart Rhythm Society recommends the use of HCQ as per the ICMR task force recommendations and strongly discourages its use for the general public without medical supervision and prescription. Even though a 12-lead ECG is a widely available tool, obtaining ECG of every suspected or confirmed patient of COVID-19 may be impractical and strain healthcare resources in a pandemic situation. Hence, using smartphone-based pocket ECG devices can potentially save healthcare resources in the current situation. The measures of restrained advocacy for potentially beneficial effects of HCQ and advice against self-medication can help prevent adverse events related to this drug.

Declaration of competing interest

None of the authors has anything to disclose.

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