Clinical Pharmacology: Advances and Applications

Dovepress
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REVIEW

Efficacy and Safety of Antimalarial as Repurposing Drug for COVID-19 Following Retraction of Chloroquine and Hydroxychloroquine

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Abstract: Various repurposing drugs have been tested for their efficacy on coronavirus disease 2019 (COVID-19), including antimalarial drugs. During the pandemic, Chloroquine (CQ) and Hydroxychloroquine (HCQ) demonstrated good potential against COVID-19, but further studies showed both drugs had side effects that were more dangerous than the efficacy. This made World Health Organization (WHO) ban the usage for COVID-19 patients. In this context, there is a need to explore other antimalarial drugs as potential therapies for COVID-19. This study provides a descriptive synthesis of clinical trials evaluating antimalarial drugs for COVID-19 treatment conducted after the withdrawal of CQ and HCQ. The method was a literature study using the keywords "antimalarial", "COVID-19", "SARS-CoV-2", "clinical trial", and "randomized controlled trial" on the MEDLINE, Scopus, and Cochrane databases. Inclusion criteria were published clinical trials with randomized controlled trials (RCTs) on the efficacy and safety of single antimalarial drugs for COVID-19, published in English and excluding combination therapies. The results showed 3 antimalarial drugs, namely Quinine Sulfate (QS), Atovaquone (AQ), and Artemisinin-Piperaquine (AP), had gone through clinical trial to assess efficacy and safety against COVID-19 patients. Out of the 3 drugs, only AP showed significant results in the primary outcome, which was the time required to reach undetectable levels of SARS-CoV-2. Furthermore, the intervention group took 10.6 days, and the control group took 19.3 days (p=0.001). Based on this review, AP showed significant potential as a therapy in the fight against COVID-19.

Keywords: randomized controlled trial, Quinine Sulfate, Atovaquone, Artemisinin-Piperaquine, SARS-CoV-2

Introduction

The Coronavirus (COVID-19) pandemic is an event in the history of the new millennium that significantly changed the global social, economic, and health landscape.[1] Since it was first reported in Wuhan, China at the end of 2019, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has rapidly spread in the world and caused a wave of infections leading to unprecedented chaos.[2] Furthermore, the rapid infection, high death rates, and widespread impacts on health systems and economies have forced countries around the world to face extraordinary challenges.[3] Efforts to understand, control, and overcome COVID-19 have become a major focus for science, governments, and global society. Therefore, study as well as development of drugs and vaccines to fight the virus have become a priority.[4,5]

COVID-19 pathophysiology involves the interaction between SARS-CoV-2 and the human host, primarily targeting the angiotensin-converting enzyme 2 (ACE2) receptor, which is highly expressed in the respiratory tract, lungs, and other tissues.[6,7] The viral entry triggers immune responses that can result in a dysregulated inflammatory cascade, often referred to as a "cytokine storm." This leads to widespread tissue damage, acute respiratory distress syndrome (ARDS),

Received: 29 August 2024
Accepted: 6 January 2025
Published: 16 January 2025

and multi-organ failure in severe cases.[8] Additionally, SARS-CoV-2 infection disrupts the renin-angiotensin-aldosterone system (RAAS), contributing to endothelial dysfunction, coagulopathy, and impaired oxygen exchange, which are hallmarks of severe COVID-19. Understanding this complex pathophysiology is critical for the identification and repurposing of therapeutic agents.

Since the outbreak, the world has witnessed efforts in study as well as development of drugs and vaccines to treat the disease. Studies have been conducted since the early phase of the pandemic, with the aim of finding effective solutions to reduce the adverse effects of the disease. At the time, there was no definitive treatment, hence, the concept of repurposing was implemented, where existing drugs were reused.[9] In this context, antimalarial drugs, such as Chloroquine (CQ) and Hydroxychloroquine (HCQ), were attracting attention due to their potency and effectiveness.[10] In fact, World Health Organization (WHO) recommended these drugs to treat COVID-19. Initial studies stated that the mechanism of action could be effective in inhibiting viral replication and calming the immune system's overreaction. Furthermore, the drugs showed potential in reducing the duration of fever, inhibiting pneumonia exacerbations, and improving lung health.[11,12]

However, subsequent research revealed significant safety concerns associated with CQ and HCQ. These drugs were found to cause severe side effects, particularly cardiotoxicity, including QT interval prolongation and an increased risk of arrhythmias, which could lead to fatal cardiac events.[13,14] Other reported adverse effects included hypoglycemia, neuropsychiatric disturbances, and gastrointestinal symptoms.[15,16] Due to these findings, WHO revoked the Emergency Use Authorization (EUA) for CQ and HCQ, emphasizing the need for safer alternatives in treating COVID-19.[17]

The continued exploration of antimalarial drugs remains significant due to their unique properties and the unmet need for effective COVID-19 treatments. Antimalarial drugs are potential candidates for use as repurposing due to the extensive evaluation for both prevention and treatment purposes, as well as their widespread utilization across diverse age groups.[18] In addition, the strong immunomodulatory and anti-inflammatory effects have good potential in fighting SARS-CoV-2.[19] Studies on other antimalarial drugs continue to be carried out in several countries. The aim was to explore the efficacy and safety of these drugs as an alternative treatment after the withdrawal of CQ and HCQ.[20–22] Various in silico and in vitro studies have been carried out to ascertain the potential of antimalarial drugs for COVID-19.[23,24]

This study aimed to provide a comprehensive review of several antimalarial drugs that had undergone clinical trials for the treatment of COVID-19. Specifically, it focused on assessing their efficacy and safety to identify potential therapeutic options. It was hypothesized that certain antimalarial drugs demonstrate measurable efficacy and safety profiles in treating COVID-19, providing a basis for their potential use as therapeutic options. Highlighting these drugs' clinical trial results not only addresses an urgent need for evidence-based treatment alternatives but also contributes to the broader understanding of repurposed drugs in managing this global health crisis.

Method

The method included conducting literature searches on the MEDLINE, Scopus, and Cochrane databases. Furthermore, relevant articles were searched using the keywords "antimalaria", "COVID-19", "SARS-CoV-2", "clinical trial", and "randomized controlled trial." This narrative review used studies and clinical trial reports published between 2019 and May 2024 on the efficacy and safety of antimalarial drugs for COVID-19. This review included randomized controlled trials (RCTs) on the efficacy and safety of single antimalarial drugs for COVID-19, published in English and only studies evaluating single antimalarial agents, without the use of combination therapies, were included to specifically assess the individual effects of these drugs. Articles that included antibiotics commonly used for malaria, such as doxycycline, were excluded. Additionally, other sources such as book chapters, conference reports, reviews, posters, articles consisting solely of abstracts, discussion results, and articles primarily focused on study design were excluded. Flow diagrams for study selection are shown in Figure 1.

Results

Several clinical trials have investigated the efficacy of different antimalarial drugs for COVID-19 following WHO's withdrawal of CQ and HCQ. Three trials were conducted using Quinine Sulfate (QS) in Indonesia, Atovaquone (AQ) in the United States, and Artemisinin-piperaquine (AP) in China. Trials on mefloquine were initiated in Japan, but there

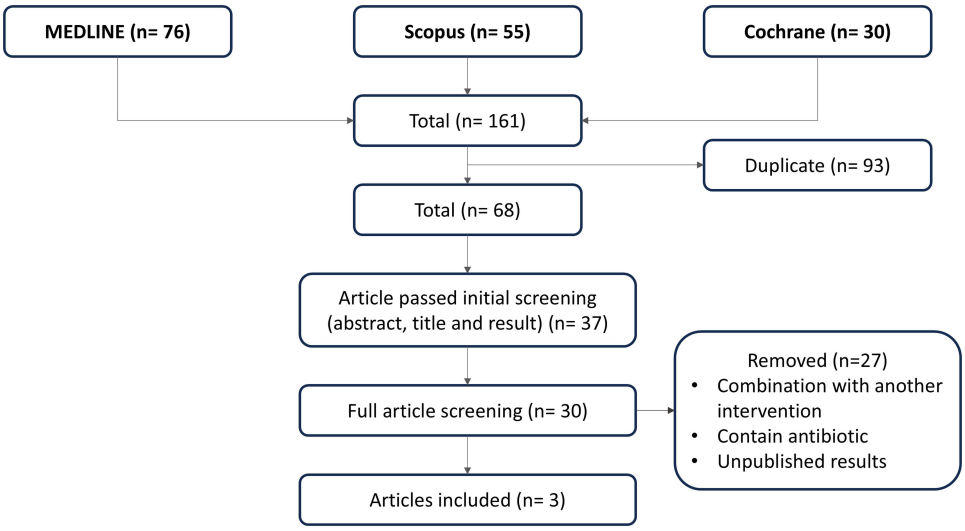

Figure 1 Flow Diagrams for Study Selection.

were no published results despite the study being registered on clinicaltrial.gov. Among the 3 antimalarial drugs studied, AP showed significant outcomes. Furthermore, patients in the intervention group had a shorter time to reach undetectable levels of SARS-CoV-2 (10.6 days vs 19.3 days in the control group). For safety analysis, AP experienced a significant increase ($p < 0.05$) in QT interval by 21.65 ms (411.94 ms before treatment and 433.59 ms after treatment). Trials of QS and AQ did not show significant differences in measured outcomes, although the intervention group showed promising results compared to the control in descriptive analyses. Efficacy of Antimalarial Drugs in COVID-19 Patients is presented in Table 1.

Discussion

Results on Clinical Trial of Antimalarial for COVID-19

Scientists are relentlessly exploring various treatment options to combat the COVID-19 virus. Among the array of potential therapies, antimalarial drugs have become intriguing candidates due to their promising properties.[25,26] This study provided a comprehensive review of clinical trial that explored the repurposing of antimalarial drugs, and offered valuable insights into their potential as therapeutic options. These trials aimed to assess the safety and efficacy of antimalarial agents such as QS, AQ, and AP in treating COVID-19 patients. Through meticulous examination of trial data, studies endeavor to elucidate clinical benefits, optimal dosage regimens, and any adverse effects associated with these drugs. Therefore, by synthesizing results from diverse trials, this review provided a comprehensive understanding of the therapeutic landscape, as well as informing healthcare practitioners and policymakers in their efforts to effectively combat the pandemic.

Quinine Sulfate (QS)

QS is antimalarial drug used for over 70 years, and the potential to fight COVID-19 has been summarized by Latarissa et al 2020.[27] Furthermore, QS is a weak base that can increase the pH of acidic intracellular organelles and interfere with the SARS-CoV-2 fusion process.[28–30] It also has a quinoline basic structure that functions to inhibit the Quinine Reductase (hQR2) enzyme and disrupt sialic acid biosynthesis. Coronavirus uses this sialic acid group as a receptor.[12,16,29,31,32] Antiviral and immunomodulatory properties are the potential of QS in fighting COVID-19 by increasing the synthesis of Retinoic acid-inducible Gene I (RIG-I) and Interferon alpha (IFN-α). These factors block the translation of viral mRNA through PKR activation and degrade viral poly mRNA by activating RNAse (L), hence, no viral protein is synthesized.[33]

Several studies have emphasized the potential of QS in vitro and in silico. A study investigated the effect of QS, CQ, and HCQ on the inhibition of SARS-CoV-2 cell replication in Vero B4 cells. The results showed inhibition of SARS-CoV-2 virus replication by QS was better than CQ and HCQ, where with 10 μM QS, virus replication could be reduced

Table 1 The Efficacy of Antimalarial Drugs in COVID-19 Patients

Author	Antimalarial Drugs	Country	Sample Size	Patient Characteristic	Design Study		Outcomes	Confidence Interval
					Control Group	Intervention Group		
[22]	Quinine Sulfate (QS)	Indonesia	25 patients (control group: 11 patients, intervention group: 14 patients)	Aged ≥18 years (up to 50 years); hospitalized for COVID-19 with mild to moderate symptoms	Standard of Care (SoC) + Placebo	• Mild case: SoC + QS 1×400 mg for 5 days • Moderate Case: SoC + QS 2×400 mg on the first day and 1×400 mg on the next day for 5–7 days	• Primary Outcome - Clinical status using a 7-point ordinal scale: NOT SIGNIFICANT • Secondary Outcomes - Incidence and duration of oxygen supplementation: NOT SIGNIFICANT - Incidence of mechanical ventilation: NOT SIGNIFICANT - Length of stay: NOT SIGNIFICANT	95%
[21]	Atovaquone (AQ)	United States	60 patients (control group: 19 patients, intervention group: 41 group)	Aged ≥18 years of age, had a positive polymerase chain reaction test for SARS-CoV-2 in 72 h of hospitalization	SoC + Placebo	SoC + Atovaquone 1500 mg BID PO for 10 days	• Primary Outcome - Log transformed viral load (copies/mL): NOT SIGNIFICANT • Secondary Outcomes - Viral load (log copies/mL) at 2, 4, and 7 days: NOT SIGNIFICANT - Area under the curve (AUC) of viral load through day 3 and 7: NOT SIGNIFICANT - Between group differences in viral load, use of remdesivir, median split of baseline values (high vs low viral load), median split time from onset of symptoms (<5 days vs >5 days, median split of body mass index (BMI), diabetes status, sex, and age: NOT SIGNIFICANT - Time to 2 log unit decrease in viral load: NOT SIGNIFICANT	Not reported

[20]	Artemisinin-Piperaquine (AP)	China	41 patients (control group: 18 patients, intervention group: 23 patients	Age ≥ 18 years, confirmed SARSCoV-2 infection in upper respiratory tract specimens by real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR)	HCQ sulfate 800 mg/day for the first 3 days, followed by 400 mg daily for the next 5 days + Arbidol hydrochloride 600 mg/day for 8 days, divided into three doses daily.	Artemisinin 125 mg and piperaquine 750 mg) for the first day and followed by a maintenance dose of one tablet/day (artemisinin 62.5 mg and piperaquine 375 mg) for the next 6 days.	• Primary Outcome - Time taken to reach undetectable levels SARS-CoV-2: Intervention group 10.6 days, control group 19.3 days (p=0.001) - Percentage of participants with undetectable SARS-CoV-2 on days 7, 10, 14, and 28: NOT SIGNIFICANT • Secondary Outcomes - The CT imaging changes within 10 days: NOT SIGNIFICANT - Corrected QT interval changes: Before treatment= 411.94 and after treatment= 433.59. The average prolongation was 21.65 ms (p=0.011) - Adverse events: NOT SIGNIFICANT - Abnormal laboratory parameters: NOT SIGNIFICANT	95%

https://doi.org/10.2147/CPAA.S493750

by 90%, while HCQ was only reduced by 50%.[34] Meanwhile, another in vitro study showed that QS had moderate antiviral activity with EC50 of 10.7 ± 3.0 μM and EC90 of 38.8 ± 34 μM in Vero E6 cells infected by SARS-CoV-2 strain (IHUMI-3).[35] In silico, QS showed strong affinity to Angiotensin Converting Enzyme-2 (ACE-2) receptor.[36–40] Another study showed affinity comparison between QS, CQ, and HCQ. The strongest binding affinity was shown by QS (−4.89 kcal.mol) and interacts with amino acids His34, Glu37, Lys353.[41]

Clinical trial of QS was conducted in Indonesia using 25 patients with mild-moderate symptoms from 2 hospitals. The primary tested parameter was clinical status using 7-point ordinal scales. Meanwhile, the secondary parameters included incidence and duration of oxygen supplementation, incidence of mechanical ventilation, and length of stay. Out of all the parameters tested, there was no significant difference between the control and the intervention group. The intervention group descriptively showed better results than the control. The small number of samples made the results show a statistically insignificant difference.[22]

While the small sample size is a limitation of the QS clinical trial, it is important to consider other potential confounding factors that may have influenced the results. Variability in baseline patient characteristics, disease severity, and concurrent treatments could also contribute to the lack of significant findings. Additionally, the study design and endpoints selected may not have been optimal to capture the therapeutic effects of QS comprehensively. Future studies with larger sample sizes and standardized protocols are necessary to account for these variables and better evaluate the efficacy of QS in COVID-19 management.

Atovaquone (AQ)

AQ is antimalarial agent that works by disrupting the mitochondrial electron transport chain in parasites and prevents their proliferation.[42] In addition to antimalarial properties, AQ has antiviral activity against a range of RNA viruses, including coronaviruses. Studies have shown that it inhibits the replication of SARS-CoV-2 in vitro by targeting a key enzyme involved in viral RNA synthesis. Furthermore, AQ showed substantial suppression of SARS-CoV-2 replication in Calu-3 cells (EC50 = 10.21 μM).[43] In a computational study investigating the binding affinity of antimalarial medications, AQ and mefloquine were the top 2 drugs in terms of their affinity towards viral proteins when compared to other compounds. Also, AQ showed significant inhibition constants for SARS HR1 spike motif protein, 3CL protease, and papain-like protease.[44] This result has sparked interest in exploring AQ as a potential therapeutic agent for COVID-19.

The mechanism of AQ in treating COVID-19 is through inhibition of purine metabolism by decreasing NT5E expression. Even though there are currently no antiviral medications designed to specifically target purine metabolism, it has been suggested as a significant target for diminishing the nucleotide pool essential for viral replication, as well as potentially producing anti-inflammatory effects.[45,46] Moreover, clinical trial of AQ has been conducted in China using 60 COVID-19 patients with a ratio between the control and the intervention group of 2:1. The primary outcome measured was log transformed viral load. The secondary outcomes included viral load, Area under the curve (AUC) of viral load through day 3 and 7, intergroup differences in viral load, use of remdesivir, median split of baseline, median split time from onset of symptoms, median split of body mass index (BMI), diabetes status, sex, age, and time to achieve a 2 log units decrease in viral load. Similar to QS, AQ clinical trial results showed no significant differences in efficacy outcomes measured between the control and intervention groups. This could be due to the small sample size. In addition, confounding variables could affect the results, as most patients in the test group had diabetes. Another factor may be that the antiviral effect of AQ was overshadowed by remdesivir which is the standard therapy used in China.[21] Similarly to QS, aside from the small sample size, the insignificant results of AQ clinical trials could also be influenced by other factors, such as the severity of symptoms in patients, the timing of drug administration after infection, and individual variations in response to therapy.

Artemisinin-Piperaquine (AP)

Antimalarial artemisinin is produced by the medicinal plant *Artemisia annua L* (*A. annua L*). It is a sesquiterpene lactone that is stored in glandular trichomes found on the plant's shoots, specifically on the leaves and flowers. For over 2000 years, the plant and artemisinin have been safely used to treat a range of fever-related illnesses, including malaria.[47]

Moreover, artemisinin derivatives are first-line treatments for malaria when used in combination with another medication, including lumefantrine or amodiaquine. These combinations are known as artemisinin-based combination therapies.[48] Additionally, artemisinins have antiviral activity, and anti-SARS-CoV-1 activity in *A. annua* extracts increased the possibility that they are active against SARS-CoV-2.[49]

Although artemisinin possesses some antiviral properties, it seems to work against anti-SARS-CoV-2 activity in hot water extracts. Also, there was an inverse relationship between the amount of artemisinin in the 8 tested cultivars of *A. annua* and the potency of the extract. It was shown that as the amount of artemisinin increased, the potency of the IC50 values decreased.[50] Further evidence for non-artemisinin anti-SARS-CoV-2 activity in Artemisia sp. was provided by Nie et al which showed that *A. afra* extracts that lacked artemisinin were equally potent against the virus as *A. Annua*.[51]

The plant *A. annua* and artemisinin decreased in vivo concentrations of inflammatory cytokines like Tumor Necrosis Factor- alpha (TNF-α) and Interleukin-6 (IL-6). These effector molecules can cause problems when SARS-CoV-2 patients experience a "cytokine storm." Additionally, artemisinin reduces fibrosis, a condition that SARS-CoV-2 survivors face, and damages organs more permanently. According to a recent report, several compounds related to artemisinin have shown some level of anti-SARS-CoV-2 activity. Dihydroartemisinin, artesunate, and arteannuin B have IC50 values less than 30 μM, while dihydroartemisinin ACTs have IC50 values between 1 and 10 μM. According to reports, artesunate's IC50 values against SARS-CoV-2 were 2.6 μM and 7–12 μg/mL (0.7–1.2 μM). Many viruses are inhibited by artemisinin, including SARS-CoV. Therefore, *A. annua* extract had shown anti-viral activity in vitro against SARS-CoV in 2005[52] and SARS-CoV-2 (EC50 value: 2.5 μg/mL).[50,53] Even though *A. annua* extracts showed some activity in vitro, artesunate 2 was found to be the most effective in inhibiting the virus.[50] Moreover, Li et al (2020) conducted a small human trial and found that artemisinin-piperaquine was safe and twice as effective as a placebo in eradicating the virus 21 days after treatment for 7 days.[20]

This study supported the results of the AP clinical trial conducted on COVID-19 patients in China with the randomized controlled trial method. Patients in the treatment group were given artemisinin 125 mg and piperaquine 750 mg for the first day followed by a maintenance dose of one tablet/day (artemisinin 62.5 mg and piperaquine 375 mg) for the next 6 days. Meanwhile, the control group was given HCQ sulfate 800 mg/day for the first 3 days, followed by 400 mg daily for the next 5 days + Arbidol hydrochloride 600 mg/day for 8 days, divided into three doses daily. Clinical trial showed significant results in the primary outcome, namely time taken to reach undetectable levels of SARS-CoV-2, where in the intervention group was 10.6 days and control was 19.3 days (p=0.001). This study showed that AP reduced the duration the virus stays in the body. Similar to the control, the intervention group showed an improvement effect on the lungs after 10 days of consumption. Therefore, this study recommended that for COVID-19 patients with mild-moderate symptoms, 8 AP tablets can be given for 7 days.[20]

AP demonstrates potential as a treatment for COVID-19, particularly in patients with mild to moderate symptoms, as evidenced by its ability to reduce duration the virus stays in the body in clinical trials.[20] However, its use must be contextualized within the broader landscape of current COVID-19 therapies, such as favipiravir and remdesivir. Favipiravir, an oral antiviral, is commonly prescribed for mild to moderate cases and has shown efficacy in reducing viral load and improving clinical outcomes.[54,55] Similarly, remdesivir is the standard of care for hospitalized patients with severe COVID-19, significantly reducing recovery time and mortality rates.[56,57] Unlike these established treatments, AP has been evaluated in limited studies with small sample sizes,[20] making its efficacy and safety data insufficiently robust to replace favipiravir or remdesivir. Moreover, AP's role might be better suited as an adjunct therapy rather than a standalone treatment. Further large-scale, randomized controlled trials are essential to determine whether AP can complement existing treatments and optimize outcomes in COVID-19 management.

Side Effects of Antimalarial Drugs for COVID-19

Antimalarial has potential side effects that need attention.[58] QS is antimalarial and also known for the use in treating leg cramps.[59] Various side effects can occur at therapeutic doses of quinine, including cinchonism (characterized by tinnitus, high-frequency hearing loss, photophobia, and other visual disturbances, dysphoria, headache, nausea, vomiting, sweating, dizziness, and postural hypotension), hypoglycemia (due to the drug's stimulatory effect on pancreatic β cells, most

common in the treatment of severe malaria), hypotension (usually associated with intravenous infusion of the drug), hearing and visual disturbances (including irreversible loss), gastrointestinal symptoms, cutaneous effects, conduction abnormalities (mild prolongation of the corrected QT interval, which is rare unless plasma levels are elevated), arrhythmias, and hemolysis (due to hypersensitivity or in patients with G6PD deficiency).[60,61] Another rare and serious side effect is immune thrombocytopenic purpura and thrombotic microangiopathy. A study by Medicare found that for every 1000 individuals consuming quinine, there were 1.67 incidents of immune thrombocytopenic purpura and 0.23 incidents of thrombotic microangiopathy.[62] Besides these side effects, QS has a good safety profile when used as directed and in the therapeutic dosage. The side effects associated with quinine use are reversible and can be resolved by stopping the medication.[27,63,64]

The most commonly observed adverse effects of AQ comprise maculopapular rash, nausea, diarrhea, and headache, occurring in 10 to 35% of individuals. A study showed that the occurrence of rash was found to be associated with elevated plasma concentrations of AQ.[65] Furthermore, AQ has the potential to cause liver problems, skin rash, and changes in blood cell count.[66] In the use of AP, common adverse effects include headache, dizziness, nausea, vomiting, anoxia, and fatigue.[67] One study found that dihydroartemisinin-piperaquine has a risk of cardiotoxicity, potentially prolonging QT interval. This study stated that unexplained sudden death may be associated with repolarization-related tachyarrhythmias following treatment with dihydroartemisinin-piperaquine, but rarely occurs. Only one instance of possible sudden cardiac death related to dihydroartemisinin-piperaquine was reported among nearly 200,000 individuals undergoing directly observed treatment with stringent follow-up.[68,69]

In AP clinical trial against COVID-19, one of the secondary outcomes was to analyze the safety by measuring ECG results before and after treatment. The results showed a significant difference in QT prolonged by 21.65 ms, with 411.94 ms before treatment and 433.59 ms after treatment, $p<0.05$. QT prolongation is due to SARS-CoV-2 infecting the endothelium and causing immune cell recruitment leading to endothelial dysfunction and extensive apoptosis. This causes the blood to become thick, and form a thrombus, as well as prolonged QT.[70] Even though the test group caused prolonged QT, it did not lead to arrhythmia and other cardiac disorders. Moreover, in patients who experience prolonged QT, their QT interval will return to normal after the drug is stopped. Monitoring should still be carried out considering the impact of AP on blood vessels.[20]

To translate these safety findings into clinical practice, specific monitoring guidelines should be established to mitigate the potential risks associated with QT prolongation during antimalarial treatment for COVID-19. Routine pre-treatment electrocardiograms (ECGs) are recommended to identify pre-existing QT prolongation or other cardiac abnormalities. Continuous ECG monitoring during treatment, particularly in patients with known risk factors such as electrolyte imbalances or concomitant use of QT-prolonging drugs, can help detect early signs of cardiac arrhythmias. Post-treatment follow-up should also be conducted to ensure the resolution of prolonged QT intervals. By integrating these monitoring strategies into clinical protocols, healthcare providers can enhance the safe use of antimalarial drugs like AP while minimizing adverse cardiac effects.

Limitations

The findings of this review are subject to several limitations. One key limitation is the heterogeneity in study populations, as the included trials involved diverse patient demographics, disease severities, and treatment settings, which may affect the generalizability of the results. Additionally, there was considerable variation in the endpoints assessed across studies, making direct comparisons and synthesis of findings challenging. Furthermore, many of the included studies had relatively small sample sizes, which could limit the statistical power to detect significant differences in efficacy and safety outcomes. These limitations highlight the need for more robust and standardized clinical trials to better evaluate the potential of antimalarial drugs in the treatment of COVID-19.

Conclusion

In conclusion, alternative antimalarial drugs were explored following the retraction of CQ and HCQ, which showed varied results. Out of the 3 clinically tested, 2 (QS and AQ) did not show significant results even though the intervention group descriptively showed better results than the control. Meanwhile, AP showed significant results in reducing the time

required to reach undetectable levels of SARS-CoV-2. However, the potential side effects of these antimalarial drugs, particularly QT prolongation with AP, warrant careful consideration. Moreover, the limited scope of evidence, including small sample sizes and the lack of diverse clinical settings, highlights the need for further research before recommending widespread use. These results showed the varying effectiveness of antimalarial treatments for COVID-19 and emphasized the potential of AP as a viable therapeutic option.

Acknowledgments

The authors would like to thank the Rector of Universitas Padjadjaran for facilitating the APC via the Directorate of Research and Community Engagement.

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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