

## BRINGING CLINICIANS TOGETHER TO DISCUSS CURRENT DRUG THERAPY

May 2020 • Vol. 17, No. 5  
Checklist

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### BEFORE THE MEETING

- Print your copy of *Prescriber's Letter Journal Club* LEADER NOTES, which will be emailed to you from *Prescriber's Letter*
- Provide the LEADER NOTES to the *Prescriber's Letter Journal Club* discussion leader
- Instruct your *Prescriber's Letter Journal Club* participants to go to [PrescribersLetter.com](http://PrescribersLetter.com) to print their PARTICIPANT NOTES. Instruct them to look for "Journal Club" on the home page or under the "Browse" heading. Be sure to tell them which month of *Prescriber's Letter Journal Club* you intend to use
- Provide instructions to your PARTICIPANTS and LEADERS about how to obtain PDFs of original articles from your local medical library (Adhere to institution's copyright policy)

### DURING THE MEETING

- Pass out any needed *Prescriber's Letter Journal Club* PARTICIPANT NOTES
- Use your *Prescriber's Letter Journal Club* LEADER NOTES to facilitate the discussion

### AFTER THE MEETING

- Go to [PrescribersLetter.com](http://PrescribersLetter.com) to learn about other topics in this month's issue, including charts, algorithms, toolboxes, etc, and listen to panelists and experts discuss our recommendations in *Emerging Recommendations Panel*

*Prescriber's Letter Journal Club. We do the digging, you do the discussing.*

### LEADER NOTES

## BRINGING CLINICIANS TOGETHER TO DISCUSS CURRENT DRUG THERAPY

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The following succinct analysis appeared in *Prescriber's Letter*. Based on vol. 27, No. 5

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### INFECTIOUS DISEASES

Patients will ask about whether hydroxychloroquine or other meds prevent or treat COVID-19 in the community.

For now, supportive care remains the mainstay of treatment.

Some meds aren't effective...such as oseltamivir or baloxavir.

And we're waiting for solid answers from ongoing studies with others...remdesivir, sarilumab, tocilizumab, etc.

So far, lopinavir/ritonavir doesn't look promising for severe COVID-19...but studies are looking at its use earlier in the course.

Chloroquine and hydroxychloroquine are in the spotlight. They're thought to prevent some viruses from multiplying...plus they have immunomodulating effects.

But put the role of these meds in perspective. Initial evidence is lab-based...with few published human trials. Expect evidence to keep trickling in.

The buzz started with a French report of 6 patients who "cleared" the virus after 6 days on hydroxychloroquine and azithromycin.

Then an observational study from the same French group concluded that most patients on the combo had a "favorable outcome."

But two small randomized trials from China found mixed results with hydroxychloroquine.

Be aware, these reports have MANY flaws...and it's too soon to say if reduced viral load correlates to COVID-19 outcomes.

Plus there's still not an optimal regimen. Doses of hydroxychloroquine vary from 400 to 800 mg/day for 5 to 14 days.

Discourage inappropriate use. Emphasize that there's no good evidence for using chloroquine, hydroxychloroquine, or azithromycin to prevent OR treat COVID-19 in the community.

For now, reserve these meds for use in a clinical trial or in hospitalized patients.

And follow your state rules, pharmacy policies, and payer guidance...many are requiring a diagnosis or days' supply limits.

Keep the risk of QT prolongation in mind, even with short-term use...especially when hydroxychloroquine is combined with azithromycin or other QT-prolonging meds.

Explain that inappropriate use may prevent others from getting these meds for lupus, rheumatoid arthritis, or malaria.

See our chart, *COVID-19 and Pharmacotherapy*, for more details...and our *COVID-19 Resource Hub* for additional resources.

*Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020 Mar 20:105949. doi: 10.1016/j.ijantimicag.2020.105949. [Epub ahead of print]*

### LEADER NOTES

## DISCUSSION QUESTIONS

### OVERVIEW OF CURRENT THERAPY

#### 1. What is known about the antiviral activity of chloroquine, hydroxychloroquine, or azithromycin?

- Chloroquine is approved to treat malaria and extraintestinal amebiasis.
- Hydroxychloroquine is the hydroxyl analog of chloroquine. It is approved to prevent and treat malaria, and is a disease-modifying antirheumatic drug (DMARD) for rheumatoid arthritis and systemic lupus erythematosus.
- There's interest in these meds as a treatment for COVID-19 since they've previously shown activity against various viruses *in vitro*, including HIV-1, hepatitis B, HSV-1, and the SARS and MERS coronaviruses.
- Limited *in vitro* data also suggests these meds may have activity versus the SARS-CoV-2 virus that causes COVID-19. Hydroxychloroquine is thought to be more potent than chloroquine versus SARS-CoV-2 based on *in vitro* data.
- In addition, hydroxychloroquine is thought to have a more tolerable side effect profile. However, QT prolongation, ocular toxicity, and serious skin reactions are concerns with either agent.
- Chloroquine and hydroxychloroquine also have immunomodulatory effects that might be beneficial to curb the inflammatory "cytokine storm" caused by COVID-19.
- Interest in the antiviral activity of azithromycin is based on *in vitro* activity against viruses such as H1N1 and Zika virus. However, there's no *in vitro* evidence of azithromycin having antiviral activity against coronaviruses, including SARS-CoV-2.
- Azithromycin has also been previously used for its immunomodulatory and anti-inflammatory effects in patients with viral respiratory tract infections.
- This study is the first to report the impact of treating COVID-19 patients with hydroxychloroquine with or without azithromycin.

### ANALYSIS OF NEW STUDY

#### 2. What type of study was this? How were the patients selected for inclusion?

- This was a single-center, open-label, non-randomized trial conducted in Marseille, France.
- Hospitalized patients with confirmed COVID-19 were included if they were over 12 years of age and had PCR documented SARS-CoV-2 at admission.
- Patients were excluded if they were allergic to hydroxychloroquine or chloroquine, or had another known treatment contraindication (e.g., retinopathy, QT prolongation, G6PD deficiency). Pregnant or breastfeeding patients were also excluded.

#### 3. How were the study groups defined? What treatment did each group receive?

- Patients in the hydroxychloroquine group were treated with 200 mg orally TID x 10 days.
- Control patients included those who refused or had a contraindication to hydroxychloroquine, as well as patients from other centers in South France.
- Symptomatic treatment including antibiotics were given at the discretion of investigators.

## LEADER NOTES

#### 4. How were the outcomes evaluated?

- The primary endpoint was virological clearance at day 6 post-inclusion based on PCR analysis of nasopharyngeal samples.
- Secondary outcomes were virological clearance over time, clinical measures such as temperature and respiratory rate, length of hospital stay, mortality, and medication side effects.
- A total of 48 patients (24 in the hydroxychloroquine group and 24 controls) was estimated to provide 85% power to detect 50% efficacy in reducing viral load at day 7 with a p-value of 0.05, assuming 10% loss to follow-up.
- Pearson's chi-square or Fisher's exact tests were used to compare categorical variables, and the Student's t-test was used to compare means.
- Patients were stratified into 3 groups based on symptoms at presentation: asymptomatic, upper respiratory tract infection (URTI), or lower respiratory tract infection (LRTI).
- Patients were seen at enrollment and daily for 14 days.

#### 5. What were the outcomes of this study?

- Twenty-six patients were enrolled in the hydroxychloroquine arm. However, 6 of these patients stopped treatment early and were lost to follow-up, leaving a total of 20 patients in the hydroxychloroquine group. Of note, 6 patients in this group were also treated with azithromycin 500 mg day 1, then 250 mg daily x 4 days.
- The control group included 16 patients.
- All included patients had at least 6 days of follow-up.
- Approximately 42% of patients were male. Patients were an average of 45 years old; however, patients in the hydroxychloroquine group were  $\approx$  51 years old versus  $\approx$  37 years old in the control group.
- About 17% of patients were asymptomatic at presentation,  $\approx$  61% had an URTI, and  $\approx$  22% had an LRTI with pneumonia confirmed by CT scan.
- The time between symptom onset and study inclusion was  $\approx$  4 days in each group.
- Overall, at day 6 post-inclusion, 14 of 20 (70%) hydroxychloroquine patients had PCR negative nasopharyngeal samples compared to 2 of 16 patients (12.5%) in the control group ( $p=0.001$ ).
- The proportion of PCR negative hydroxychloroquine patients was significantly higher than controls when nasopharyngeal samples were compared at days 3, 4, and 5.
- All patients who received hydroxychloroquine and azithromycin had negative nasopharyngeal samples at day 6 compared to 57.1% of patients who received hydroxychloroquine only ( $p<0.001$ ).
- Investigators note that the "drug effect was significantly higher in patients with URTI and LRTI, as compared to asymptomatic patients." However, supportive data were not given.
- Results of secondary outcomes (e.g., hospital length of stay, mortality) were not reported.

### LEADER NOTES

**6. What were the strengths and weaknesses of this study?**

- Although this open-label, non-randomized study provides preliminary evidence about the impact of hydroxychloroquine (+/- azithromycin) in patients with COVID-19, there are a plethora of limitations and many questions related to study integrity.
- This study is the first to report on the impact of treating COVID-19 patients with hydroxychloroquine with or without azithromycin. It served as a catalyst related to the use of these meds to treat COVID-19 due to misinterpretation and overgeneralization of study results. For example, the results of this study were generalized by many as support for use of hydroxychloroquine to *prevent* COVID-19, even though this use was not studied. Additionally, results of this study are mostly relevant to patients with mild or moderate symptoms of COVID-19, since little over 20% of patients had LRTI at baseline.
- It is understandable that in extenuating circumstances such as the COVID-19 pandemic, researchers are working to disseminate information quickly. However, this comes at the cost of relaxed standards for study methods and reporting, along with limited peer review or other means to ensure scientific rigor. For example, this study was first released on March 16, 2020 as a “preprint” that had not yet been peer reviewed. It was then published online on March 20<sup>th</sup>, which still allowed very limited time for review prior to publication.
- In fact, the International Society of Antimicrobial Chemotherapy, which is the professional society that publishes the International Journal of Antimicrobial Agents (IJAA), has issued a statement of concern that “the article does not meet the Society’s expected standard” due to insufficient explanation of inclusion criteria and measures to ensure patient safety. It is also important to note that one of the authors of this study is the Editor-in-Chief of IJAA (J.M. Rolain from Marseille, France). However, it is noted that J.M. Rolain had no involvement in the peer review of the article.
- Investigators note that 6 hydroxychloroquine patients were lost to follow-up, citing that 3 of these patients were transferred to the ICU, 1 died, 1 left the hospital, and 1 stopped treatment due to nausea. The fact that data from patients who transferred to the ICU or died was excluded is especially concerning, since excluding possible treatment failures skews study results toward favorable effects.
- The primary outcome of this study was nasopharyngeal viral clearance, which is a surrogate endpoint. However, it is uncertain whether this will ultimately correlate with clinical outcomes.
- Further, investigators do not describe the sensitivity or specificity of their test, meaning that we’re unsure how often PCR results were false negatives or false positives. In looking at the supplementary table that’s available from the publisher’s site, several patients had PCR results that went from negative back to positive on subsequent days. It also appears that a different PCR test may have been used for some control patients, as these results are described differently in the supplementary table.
- Additionally, there were more “missing” PCR results in the control group compared to patients in the hydroxychloroquine group. Almost 40% of PCR results had to be imputed in the control group versus about 5% in the hydroxychloroquine group. It is also notable that 1 patient in the hydroxychloroquine group and 5 in the control group did not have PCR results on day 6. It is unclear how these patients were “counted” in day 6 results.

## LEADER NOTES

- The only baseline characteristics given are age, sex, category of symptoms, and time between onset of symptoms and study inclusion. However, patient comorbidities, which have been shown to impact patient outcomes in patients with COVID-19, were not given. This makes it impossible to compare whether patients were equally “sick” and could lead to confounding due to differences in baseline characteristics.
- In addition, because the study was open-label, selection bias could've impacted whether patients were treated with hydroxychloroquine +/- azithromycin. For example, “sicker” patients could've been more likely to receive treatment. Conversely, patients with baseline comorbidities such as CV disease may have been less likely to receive either of these medications due to concern for QT prolongation. Finally, there was no criteria defined for why certain patients were also treated with azithromycin.
- It is unclear whether results were after 6 days of treatment or after 7 days, or if patients were followed beyond this period. Study power was cited to be based on results at day 7, and investigators cite that patients were to be followed for 14 days. However, results were given only up to day 6. (It could be that study day 0 was “counted” as a treatment day, making day 6 actually the 7<sup>th</sup> day of treatment.) Further, patients were to receive treatment for 10 days even though outcomes were reported at day 6 (or 7). There is no explanation for why data beyond day 6 is not given.
- Similarly, authors cite that secondary outcomes included virological clearance over time, clinical measures such as temperature and respiratory rate, length of hospital stay, mortality, and medication side effects. However, none of these outcomes are described in the study publication. Of note, reports of QT prolongation with hydroxychloroquine are beginning to surface in ongoing trials of its use for COVID-19.
- Study methods cite that only patients over 12 years of age were to be included in the study. However, review of the data supplement revealed that two 10-year-old patients and one 12-year-old patient were included in the control group.
- This study was funded by the French government. Therefore, bias due to the influence of study sponsors isn't likely.

#### **7. Were the results expressed in terms we care about and can use?**

- Not really. The outcome of this study was nasopharyngeal viral clearance, which is a surrogate endpoint. It is uncertain whether this will correlate with clinical outcomes. In addition, there are known risks with hydroxychloroquine +/- azithromycin; however, adverse effects of treatment were not reported.

### HOW SHOULD THE NEW FINDINGS CHANGE CURRENT THERAPY?

#### **8. Do the results change your practice? How?**

- No. The many limitations of this study raise serious concerns about whether we can believe the data.
- In addition, there is still no evidence about the impact of hydroxychloroquine +/- azithromycin in ambulatory patients with COVID-19 or for prophylaxis.
- Inappropriate use may prevent patients from getting hydroxychloroquine for lupus, rheumatoid arthritis, or malaria.
- Find COVID-19 studies open to enrollment in your area at [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

### LEADER NOTES

## APPLY THE NEW FINDINGS TO THE FOLLOWING CASE

JP is a 67-year-old African American male who is in clinic today for follow-up of newly diagnosed type 2 diabetes. His past medical history is also significant for hypertension, stable CAD, and obesity. JP is a nonsmoker and reports minimal alcohol use. JP is taking amlodipine 10 mg daily, aspirin 81 mg daily, atorvastatin 80 mg daily, lisinopril 20 mg daily, and metformin ER 1,000 mg daily.

JP says he's feeling better than he did at his last appointment with you 6 weeks ago and is tolerating metformin well. He's also been cutting back on carbs and trying to get outside for a 30-minute walk at least once a day.

Today, JP's vitals are BP 132/84 mmHg, HR 74, O<sub>2</sub> sats 98% on room air, BMI 34. His A1C is currently 8.2% (down from 8.7% at diagnosis).

### 9. How should you manage JP's diabetes today?

- ADA recommends an A1C goal of < 7% in many patients with diabetes to reduce microvascular complications (retinopathy, nephropathy, neuropathy). However, this goal does not seem to reduce macrovascular events (e.g., MI or stroke) or death.
- A higher goal such as 7.5% to 8% may be more appropriate in patients over 65, those with long-standing diabetes, or patients with chronic conditions.
- Metformin monotherapy can lower A1C around 1%. Aim for a target dose of 2 g/day.
- Lifestyle changes such as aiming for a healthy weight, regular physical activity, and smoking cessation should be encouraged.

You commend JP for adhering to metformin and for working to make lifestyle changes that will help manage his diabetes. You reinforce your prior discussion about A1C goals and suggest that a reasonable goal for JP is somewhere between 7.5% and 8%. You recommend increasing his metformin to 1,000 mg twice daily.

JP brings up that he is concerned about he or his wife contracting COVID-19. He said he's been watching the news and knows that they are both at higher risk of having complications from COVID-19 due to their age and health conditions (his wife also has diabetes). He's heard the talk about hydroxychloroquine and also about various supplements to "boost the immune system." He asks if he and his wife should take something to prevent getting COVID-19.

### 10. What should you discuss with JP about hydroxychloroquine or supplements to prevent COVID-19?

- Chloroquine and hydroxychloroquine are thought to limit viral replication. They also have effects that may help limit the severe inflammatory response that may be harmful in patients who get COVID-19.
- So far, most evidence comes from the lab and there's few published studies in humans. In addition, the studies currently published in humans have many flaws.
- There are currently no published studies using chloroquine or hydroxychloroquine to prevent getting COVID-19.

## LEADER NOTES

- Although risks aren't being discussed as much in media reports, serious concerns with chloroquine and hydroxychloroquine include QT prolongation, ocular toxicity, and serious skin reactions.
- There's no good evidence that supplements such as vitamin C, vitamin D, zinc, echinacea, or garlic prevent COVID-19 or other viruses. But it's generally okay if patients want to try them.

You discuss the limitations of the current data with hydroxychloroquine and bring up that it also has serious risks. You also discuss that there's no good evidence that popular "immune boosting" supplements prevent COVID-19 or other viruses, but they're okay to try.

You advise that the best way for JP and his wife to avoid contracting COVID-19 is through frequent handwashing with soap and water for at least 20 seconds, staying home as much as possible, and "social distancing" from others if it is absolutely necessary to go out.

You bring up that CDC now recommends wearing a cloth face cover when it is necessary to go out in public (e.g., to the grocery store). However, you reinforce that this is to protect other people in case you are infected and is NOT a substitute for social distancing.

JP also asks if it's true that taking lisinopril may make him more susceptible to getting COVID-19.

**11. What should you discuss with JP about ACEIs and ARBs in the context of COVID-19?**

- There are speculative reports that taking an ACEI or ARB may increase the risk of getting COVID-19 or having serious complications from it, since the virus that causes COVID-19 gets into cells via ACE2 receptors, and ACEIs or ARBs may upregulate ACE2.
- The risk is hypothetical at this point. There's currently no evidence that taking an ACEI or ARB increases the risk of getting COVID-19 or having a serious infection.
- Researchers are actually starting to study whether the ARB losartan may make COVID-19 less severe. But we won't have this evidence for a while.

You counsel JP that this risk is hypothetical and that there's currently no evidence that lisinopril or any other ACEI or ARB increases the risk of getting COVID-19 or having a more serious infection. You encourage JP to continue his current BP regimen since his BP is under control.

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LEADER NOTES

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**Additional Prescriber's Letter Resources available at PrescribersLetter.com**

- Chart, COVID-19 and Pharmacotherapy. *Pharmacist's Letter/Prescriber's Letter*. May 2020.
- Chart, Supplements for Colds and Flu in Adults. *Pharmacist's Letter/Prescriber's Letter*. January 2020.
- Chart, Antivirals for Influenza. *Pharmacist's Letter/Prescriber's Letter*. December 2019.
- Chart, Treatment of Cough in Adults. *Pharmacist's Letter/Prescriber's Letter*. January 2018.
- Chart, Drugs for Type 2 Diabetes. *Pharmacist's Letter/Prescriber's Letter*. July 2019.

## LEADER NOTES



*Toolbox, Improving Diabetes Outcomes. Pharmacist's Letter/Prescriber's Letter. March 2019.*

*Commentary, Improving Tolerability to Metformin. Pharmacist's Letter/Prescriber's Letter. December 2015.*

*Toolbox, Optimizing Care of Patients with Coronary Artery Disease. Pharmacist's Letter/Prescriber's Letter. February 2018.*

*Chart, Treatment of Hypertension in Coronary Artery Disease. Pharmacist's Letter/Prescriber's Letter. June 2015.*

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## LEADER NOTES