

The great fall of chloroquine- lessons learned from the pandemic

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Abstract

Drugs like chloroquine (CQ)/ Hydroxy chloroquine (HCQ) had been widely used as treatment options at the start of pandemic with little supporting evidence. American Thoracic Society (ATS) led International Task Force had come up with some important 'suggestions' regarding CQ/ HCQ usage initially. They have suggested to use these drugs in covid 19 patients with severe pneumonia on a case by case basis. However, the role of HCQ prophylaxis, the effect of combination with macrolides, benefit versus risk assessment, age group profile and the exact definition of severe pneumonia remain unanswered among others. Now, it had become quite obvious that our perceptions based on some observational studies were completely wrong.

Keywords: COVID 19; Chloroquine (CQ)/ Hydroxy Chloroquine (HCQ); American Thoracic Society; Pneumonia; Macrolides; QT Prolongation

1. Introduction

COVID 19 had already affected almost all countries/ territories worldwide since its origin in 2020 [1]. COVID 19 treatment strategy had made considerable progress by now and mortality rates are coming down. From the initial estimation of around 2% mortality rate, it has gone as high as 10% in certain countries. Till now, we had been left with preventive strategies only like universal hand washing, masking and social distancing [2]. The wonder drug for cure of pandemic still remain elusive.

1.1. Why this review?

Different individuals/ establishments were coming up with various clinical combinations and claiming success for the same. The best example would be chloroquine (CQ)/ Hydroxy chloroquine (HCQ), an age old drug for treatment of malaria. Since it was a long-forgotten disease in the west, the drug also lost its charm except may be for some autoimmune diseases [3].

It was at this crucial juncture that American Thoracic Society (ATS) led International Task Force had come up with some important 'suggestions' on April 3, 2020, regarding chloroquine/ Hydroxy chloroquine (HCQ) usage [4]. They were also hesitant to use the term 'recommendation' because direct evidence was scarce at that point of time. Since this was probably the first attempt by a major international body on chloroquine (CQ)/ Hydroxy chloroquine (HCQ), the salient features of these suggestions should be discussed in detail.

2. Chloroquine (CQ)/ Hydroxy chloroquine (HCQ), the key questions

The key questions to be addressed were:

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- Whether it was useful in covid -19 positive out-patients?
- What was the role of CQ/HCQ in covid -19 positive inpatients with no radiologic evidence of pneumonia?

For both covid -19 positive outpatients and inpatients with no radiologic evidence of pneumonia, the American Thoracic Society panel made no suggestion for or against CQ/ HCQ usage [4]. At that time, there were no international guideline to support its usage in out-patients with covid-19 positivity. This also applied to those patients who were on treatment at home for mild disease. So it should be concluded that chloroquine (CQ)/ Hydroxy chloroquine has no role in the treatment of either out-patient or inpatients with no radiologic evidence of pneumonia. Additionally, concerns were raised about this drug being used for prophylaxis.

- Was there any role for chloroquine (CQ)/ Hydroxy chloroquine (HCQ) prophylaxis? [5].

This topic needed to be dealt with in detail because even some national societies were recommending chloroquine (CQ)/ Hydroxy chloroquine (HCQ) prophylaxis in select subset of population [6]. There was no mention regarding prophylactic use in that ATS suggestions. Given the potential adverse event profile of these drugs, this question needed urgent clarification. Sanket Shah et al, in their review article had stated that no articles were available to define the role of chloroquine prophylaxis in covid-19. They had even alerted the possibility of having a false sense of security after consuming this drug [7]. As of then in April 2020, there were no clear cut recommendations favouring the use of chloroquine (CQ)/ Hydroxy chloroquine (HCQ) as a prophylactic drug in covid-19.

- Role of CQ/HCQ in covid positive pneumonia?

No large randomized control trials were available at that time to conclusively suggest a recommendation for or against CQ/HCQ. Many experimental therapies were done across the world with these drugs [8]. These might be justified based on the seriousness of the disease and urgency of the pandemic. Based on the available evidence at that point of time, ATS led international panel suggested that CQ/ HCQ might be used in covid-19 positive severe pneumonia on a case by case basis. Hence it was postulated that chloroquine (CQ)/ Hydroxy chloroquine (HCQ) might be tried in hospitalised patients with COVID- 19 positive pneumonia.

3. Unanswered questions

- CQ/ HCQ was notorious to cause QT interval prolongation, hepatic and renal complication [9]. When used in combination with other drugs like macrolides, these adverse events were likely to worsen. The suggestions from the ATS panel were silent in this regard. They should have looked into the benefits of this combination also (CQ and macrolides) [10]. Till date, there is no definite answer for the rationale of this combination though it is widely used in certain parts of the world.
- Do the benefits outweigh the potential risks of CQ/ HCQ?

This question was clearly not answered in that ATS led International Task Force suggestions. Whether the risk benefit ratio favoured the usage of these drugs remained to be evaluated.

- Was it safe to be used in children?

A suggestion into the possible age group (or a cut-off age) where CQ/ HCQ could be used should be included in any future guidelines.

- What was the exact mechanism of action of this drug in covid-19?

The mechanism of action of CQ/ HCQ on COVID 19 pneumonia was not clear at all. Whether it was due to immunomodulatory effect or change in viral load remain unknown [11]. The future guideline panel should look into this matter in detail so as to boost the clinician's confidence in any particular drug.

- Which drug to be chosen among the two?

This question has not been addressed in any of the available guidance. The specific indication for each of these two drugs should be known so that they could be used in any indication in future more judiciously.

- Could it be used for all covid- 19 pneumonia cases?

The term pneumonia itself is a very broad topic. ATS panel has suggested the usage of chloroquine in “severe pneumonia”. But the term “severe pneumonia” is rather vague. The future recommendations should have made a clear definition for ‘severe pneumonia’ so that patient selection would have much easier and randomized trials could be performed.

4. The inevitable ‘fall’

On 17 June 2020, WHO made an announcement that the hydroxychloroquine (HCQ) arm of the Solidarity Trial to find an effective treatment for COVID-19 was withheld? The data from the trial arm showed that hydroxychloroquine did not result in the reduction of mortality of hospitalised COVID-19 patients, when compared with the routine standard of care. The practice of using hydroxychloroquine for prevention had little or no effect on preventing illness, hospitalization or death from COVID-19. Also, hydroxychloroquine might increase the risk of diarrhoea, abdominal pain, nausea, headache and drowsiness [12].

National Institutes of Health, in its update on July 2021, recommended against the use of chloroquine or hydroxychloroquine and/or azithromycin for the treatment of COVID-19 in hospitalized as well as non-hospitalized patients. Both of these drugs had similar toxicity profiles, although hydroxychloroquine is better tolerated and had a lower incidence of toxicity than chloroquine. Cardiac adverse events included QTc prolongation, Torsades de Pointes, ventricular arrhythmia, and cardiac deaths. The use of azithromycin was also associated with QTc prolongation and its combination with hydroxychloroquine had been associated with still higher incidence of QTc prolongation and cardiac adverse events in patients with COVID-19 [13].

Cochrane review addressed the question of whether chloroquine or hydroxychloroquine was useful in treating people with COVID-19, or in preventing infection in people who had been exposed to the virus. They concluded that HCQ neither reduced mortality nor decreased the requirement of mechanical ventilation. They also suggested against starting new studies with HCQ in the management of COVID 19 [14].

Abbreviations

- CQ: chloroquine
- HCQ: Hydroxy chloroquine
- ATS: American Thoracic Society

5. Conclusion

The ATS led International Task force had definitely made the first step towards addressing the vexed question of CQ/HCQ usage in COVID 19 at the beginning of the pandemic. It should be the first major international society to bring out such a guidance in those troubled times. However, the later studies had shown conclusively that our hopes were misplaced. The idea of having a cheaper drug as the quick- fix remedy to the pandemic was completely erratic. The tendency to jump upon the conclusions of observational trials rather than wait for controlled trials proved to be wrong. The pandemic once again underscored the value of evidence- based medicine as the cornerstone of modern medicine.

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