FDA REGULATORY TOOLBOX FOR COVID-19 RESPONSE
RESEARCH HIGHLIGHTS: REMDESIVIR, HYDROXY/CHLOROQUINE
UPDATES FROM THE FRONT LINES: FLORIDA & INDIA

APRIL 22, 2020
WEBINAR SERIES PARTNERS

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DIDACTIC SPEAKERS

FDA REGULATORY TOOLBOX FOR COVID-19 RESPONSE

- Elizabeth Sadove, JD
- Director of Medical Countermeasures Regulatory Policy, Office of Counterterrorism and Emerging Threats, Office of Chief Scientist, Office of the Commissioner, U.S. Food & Drug Administration

RESEARCH HIGHLIGHTS: REMDESIVIR, HYDROXYCHLOROQUINE & CHLOROQUINE

- Charles McKay, MD, FACMT, FACEP
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- Associate Medical Director, Connecticut Poison Control Center
- Associate Clinical Professor, University of Connecticut School of Medicine, Farmington, CT
NONE OF OUR SPEAKERS HAVE ANY CONFLICTS OF INTEREST TO DISCLOSE
FDA REGULATORY TOOLBOX
FOR COVID-19 RESPONSE

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The views expressed in this presentation are those of the presenter and do not necessarily represent those of the U.S. Food and Drug Administration nor should they be interpreted as official Agency policy.
LEGAL/REGULATORY MECHANISMS FOR EMERGENCY USE OF MCMS

- **Expanded Access (EA) to Investigational Drugs and Devices**
  - FD&C Act § 561
  - Investigational New Drug Application (IND) (21 CFR Parts 312.300-320)
  - Investigational Device Exemption (IDE) (21 CFR Part 812)

- **Emergency Use Authorization (EUA)**
  - FD&C Act § 564

- **Other Emergency Use Authorities**
  - FD&C Act §§ 564A, 505-1, and 564B
FOR MORE INFORMATION

- Latest FDA Information on COVID-19 response
  - Device Updates: [https://www.fda.gov/media/136702/download](https://www.fda.gov/media/136702/download)
  - Serological Tests: [https://www.fda.gov/media/137111/download](https://www.fda.gov/media/137111/download)
  - Therapeutic Updates: [https://www.fda.gov/media/136832/download](https://www.fda.gov/media/136832/download)

- MCM Emergency Use Authorities Website
THANK YOU

PLEASE REACH OUT WITH ANY QUESTIONS

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CHLOROQUINE: EARLY REPORT FROM CHINA

- By mid-February “…more than 10 hospitals in Wuhan, Jingzhou, Guangzhou, Beijing, Shanghai, Chongqing, and Ningbo (5). Thus far, results from more than 100 patients have demonstrated that chloroquine phosphate is superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus negative conversion, and shortening the disease course according to the news briefing. Severe adverse reactions to chloroquine phosphate were not noted in the aforementioned patients.”

- Of the 15 prospective studies identified in the letter
  - Six have been cancelled for lack of enrollment
  - Seven have no control group; 6 of these compare various doses of HCQ or CQ, and/or arms with anti-viral agents (lopinavir, ritonavir, etc.)
  - Three study mild disease only; many exclude underlying cardiac disease or prolonged QTc interval; most exclude co-existing CKD-stage 4 or dialysis, liver disease (>2-5 x ULN ASAT), and various other chronic conditions

- There are an additional 10 studies listed on the clinical trials site since mid-February (2 cancelled, 1 without control group, 1 retrospective, and 1 is a questionnaire assessing infection in those already on HCQ for auto-immune diseases).

- Of the potentially 14 prospective studies underway with either control groups or comparative arms:
  - Exclusion criteria also specifically include: age over 65, 70 or 75 (7 studies), QTc prolongation at entry (5 studies)
  - Outcomes range from time to symptom or fever improvement to biomarker improvement to negative viral studies to discharge/recovery status
  - The proposed recruitment (through May) is: approximately 560 HCQ, 712 CQ, and 740 “control” or non-HCQ/CQ patients
HYDROXYCHLOROQUINE: UPDATE FROM MARSEILLE

- Initial report of 20 patients with mild disease treated with 600mg HCQ (200mg tid for 10 days) demonstrated viral clearance (negative nasopharyngeal PCR) by day 6 in 70% vs 12.5% of 16 controls; all 6 of the 20 treated with both HCQ and Azithromycin (5 day course) were negative.

- Follow-up report of 80 patients (including the 6 from 1st report):
  - Median age 52 yrs; 46 of 80 with ≥1 chronic condition; ECG before treatment and on Day2
  - Low NEWS (69 of 75 scored 0-4) – 12 given supplemental oxygen; <½ with lower pulmonary complaints or pneumonia

- “By administering hydroxychloroquine combined with azithromycin, we were able to observe an improvement in all cases, except in one patient who arrived with an advanced form, who was over the age of 86, and in whom the evolution was irreversible. For all other patients in this cohort of 80 people, the combination of hydroxychloroquine and azithromycin resulted in a clinical improvement that appeared significant when compared to the natural evolution in patients with a definite outcome, as described in the literature. In a cohort of 191 Chinese inpatients, of whom 95% received antibiotics and 21% received an association of lopinavir and ritonavir, the median duration of fever was 12 days and that of cough 19 days in survivors, with a 28% case-fatality rate... A study conducted in 76 Chinese COVID-19 in patients showed that high viral RNA load is associated with the severity of the disease.”

Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: an observational study

Running title: Hydroxychloroquine-Azithromycin and COVID-19

Philippe Gautret1,2, Jean-Christophe Lagier1,3, Philippe Parola1,2, Van Thuan Hoang1,2,4, Line Meddeb1, Jacques Sevestre1, Morgane Maille1, Barbara Doudier1, Camille Aubry1, Sophie Amrané1, Piseth Seng1, Marie Hocquart1, Julie Finance2, Vera Esteves Vieira1, Hervé Tissot Dupont1,3, Stéphane Honore4,5, Andreas Stein1,3, Matthieu Million1,3, Philippe Colson1,3, Bernard La Scola1,3, Véronique Vein4, Alexis Jacquier5, Jean-Claude Deharo1, Michel Drancourt1,3, Pierre Edouard Fournier1,2, Jean-Marc Rolain1,3, Philippe Brouqui1,3, Didier Raoult1,3,6.

IHU-Méditerranée Infection, Marseille, France.
HYDROXYCHLOROQUINE: USA V.A. SYSTEM

Retrospective study of 368 PCR+ VA inpatient men (med. age 69, med. BMI 30, male, ⅔ African-American) admitted between Mar 9-Apr 11

- Distribution: 97 HCQ, 113 HCQ+Azithro, 158 no HCQ (⅓ Azithro)
- Mortality: 27.8% HCQ, 22.1% HCQ+Azithro, 11.4% no HCQ (p=0.003)
- Mech.Vent: 13.3% HCQ, 6.9% HCQ+Azithro, 14.1% no HCQ (p=0.547)

The HCQ group was sicker acutely (VS, labs) and chronically (CVD)

- Propensity score adjustment using multinomial logistic restricted cubic spline regression revealed that none of the 47 demographic, clinical, or laboratory characteristics accounted for the adjusted hazard ratio for death of 2.61 (1.10-6.17) in the HCQ-treated group vs 1.14 (0.56-2.32) in the HCQ+Azithro group

Questions?

- Since no change in likelihood of mechanical ventilation in sicker group, did HCQ treatment actually improve condition until death? What was the prevalence of DNR designation? ECG analysis is not described.
- Symptom onset comparable?...Dose, duration, and completion of therapy?...
- What about secular trends – treatment dates cross reports, such as Raoults(!)
**CHLOROQUINE: BRAZIL**

- Interim safety report on group of 81 hospitalized patients treated with azithromycin and ceftriaxone for COVID-19 pneumonia/ARDS (90% also treated with oseltamivir)

- Randomized to chloroquine 450mg daily (for 4 days after loading dose of 900mg) or an intended course of 10 days of 1200mg
  - Mortality of 27%, higher in higher dose group (39% vs 15%; p=0.03) with no evidence of more rapid viral clearing (by day 4)
  - The 5 patients over age 75 were all in the high dose group; 2 of the deaths were in this older age group
  - Two patients in the high dose group developed ventricular tachycardia
  - Increase in QTc>500msec (19% vs 11%; p=0.51) in higher dose group

- The higher dose treatment arm was stopped; remainder of study ongoing
Report of open-label administration of remdesivir (200mg followed by 100mg daily for up to an additional 9 days; completed in 75%) in 53 of 61 hospitalized COVID-19 patients demonstrating room air O2sat <94%, followed to outcome as of 28 days

- Median age 62 (range 23-82yrs), 68% with co-existing conditions; 57% mechanically ventilated and 8% on ECMO for a median of 2 days before treatment begun (IQR: 1-8days)
- After more than 2 weeks follow-up, 68% of patients improved, while 15% worsened in terms of oxygen/support requirements
  - More than ½ (57%) of the intubated patients were extubated
  - Three of the 4 patients were able to come off ECMO
  - By 4 weeks follow-up, 84% were significantly improved or discharged; 13% had died
- “Interpretation of the results of this study is limited by the small size of the cohort, the relatively short duration of follow-up, potential missing data owing to the nature of the program, the lack of information on 8 of the patients initially treated, and the lack of a randomized control group. Although the latter precludes definitive conclusions, comparisons with contemporaneous cohorts from the literature, in whom general care is expected to be consistent with that of our cohort, suggest that remdesivir may have clinical benefit in patients with severe Covid-19.”
WHAT CAN WE TAKE AWAY FROM THESE STUDIES?

- Hydroxychloroquine appears to be tolerated in younger patients with mild illness, particularly when caution is taken to avoid co-prescribing QTc interval-prolonging medication.

- Although the ages of the two groups were not matched, the Brazilian report suggests that caution is warranted for higher doses – or the accumulation of – chloroquine (and by association, hydroxychloroquine), particularly in elderly patients and those with severe COVID-19 infections.

- The more rapid viral clearance described in the Marseille papers is not supported by the findings in the more severely ill patients described in the Brazilian paper.

- The NEJM remdesivir report lacked a control group, but the recovery from very severe illness is notable. Remdesivir demonstrated no harm in the doses used.

- As more papers flood the internet in non-peer reviewed/non-standard format, reported data must include information regarding comparable severity of illness and indications for treatment when “historic” comparisons are used.

“When someone gives an ‘antidote’ and the patient doesn’t die, the only thing that has really been demonstrated is that the treatment didn’t kill the person.”

(paraphrase from Findley E. Russell MD, PhD: Snake Venom Poisoning, 1983)
THANK YOU
PLEASE REACH OUT WITH ANY QUESTIONS

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ON-DEMAND RESOURCES

All webinars are recorded and posted to the ACMT website: www.acmt.net/covid19web

Questions?
Write to: info@acmt.net
ACMT COVID-19 Web Series FAQs

Chloroquine and Hydroxychloroquine

There has been a lot of interest in certain anti-microbials' effectiveness in decreasing viral load and shortening time of symptoms from COVID-19 infection. On April 3, 2020, the United States Food and Drug Administration (FDA) issued an “Emergency Use Authorization” (EUA) for chloroquine and hydroxychloroquine. Small studies have also evaluated use in combination with the macrolide, azithromycin. Concerns about medication safety, maintaining availability for already approved indications, and the reliability or applicability of the science regarding efficacy combine to make this a difficult and evolving situation. Please access the ACMT Webinar series and other resources in ACMT Response to COVID-19. Frequently Asked Questions will be added on these pages as the series continues.

FAQs - Chloroquine and Hydroxychloroquine

Last updated: April 15, 2020

- How effective are chloroquine, hydroxychloroquine, or azithromycin in COVID-19?
- What are the recommended doses of Chloroquine or Hydroxychloroquine for COVID-19?
- What kind of monitoring should be done for people taking chloroquine or hydroxychloroquine for COVID-19?
NEXT WEBINAR

TESTING, TESTING, TESTING

Nicole D. Pecora, MD, PhD
Associate Director, Microbiology Laboratory
University of Rochester Medical Center

Wednesday, April 29, 2020
3:00 PM EDT

www.acmt.net/covid19web