What are the data regarding use of hydroxychloroquine sulfate (Plaquenil®) in combination with azithromycin (Zithromax®/Z-Pak®) for the treatment of COVID-19?

Initial response: March 25, 2020
Update 3: April 26, 2020

Summary of changes:

- Limited data are emerging from mostly unpublished retrospective studies investigating the use of hydroxychloroquine (HCQ) with or without azithromycin (AZ) for treatment of patients with COVID-19.
- This update includes selected results of identified studies that evaluated the combination of HCQ+AZ.

Selected studies evaluating HCQ+AZ for treatment of COVID-19:

Reference	Study design	Population	Treatment regimens	Results
Molina et al	P cohort in France	n=11 adults; 7 m, 4 f; mean age 58.7 y, 8 with significant comorbidities	HCQ 600 mg/d x 10 days + AZ 500 mg x day 1, 250 mg/d x days 2-5	Day 0: 10/11 had fevers and were on nasal oxygen. Day 5: 1 died, 2 transferred to ICU, 1 had discontinued treatment due to QT prolongation. Days 5-6: (+) nasopharyngeal swabs in 8/10.
Gautret et al	P cohort in France	n=80 adults;* 53.8% m, median age 52 y, 57.5% with ≥1 risk factor for severe COVID-19	HCQ 200 mg TID x up to 10 days + AZ 500 mg x day 1, 250 mg/d x days 2-5; ceftriaxone added for 18 patients with PNA and higher risk scores	On admission, 92% scored low risk for clinical deterioration; 53.8% had CT evidence of PNA. During treatment, 12 patients required oxygen therapy, 3 transferred to ICU, 1 died, and 65 (81.3%) were discharged. Mean length of stay was 4.6 ± 2.1 d.
Articles pre-print and not peer-reviewed				
Million et al**	R cohort in France	n=1061 adults with ≥3 days of treatment and ≥9 days of follow-up; 46.4% m, mean age 43.6 y	HCQ 200 mg TID x up to 10 days + AZ 500 mg x day 1, 250 mg/d x days 2-5; ceftriaxone or ertapenem added for patients with PNA and higher risk scores (number not specified)	On admission, 95% scored low risk for clinical deterioration; 65.7% had CT evidence of PNA. 91.7% (973) had a good clinical outcome; 4.3% had a poor outcome (10 transferred to ICU, 8 died, 31 hospitalized for ≥10 days). Factors associated with poor outcome: OR, 95% CI • Older age: 1.11 (1.07-1.15) • Selective βblocker use: 4.16 (1.19-14.55) • ARB use: 18.40 (6.28-53.90) • High/medium risk scores: 10.05 (3.16-32.02)
Magagnoli et al	R cohort in US VA MCs	n=368 adults; 100% m, median age 65 y	3 cohorts: HCQ (n=97) HCQ+AZ (n=113) No HCQ (n=158) Doses not specified	Baseline characteristics comparable; HCQ+AZ more likely to be given to sicker patients. HCQ vs. HCQ+AZ vs. no HCQ: • Death rates: 27.8% vs. 22.1% vs. 11.4% • Mech ventilation: 13.3% vs. 6.9% vs. 14.1% Risk of death (adjusted HR (95% CI)): • HCQ vs. no HCQ: 2.61 (1.10-6.17) • HCQ+AZ vs. no HCQ: 1.14 (0.56-2.32)
Chorin et al	R cohort at NYU Langone MC, evaluating change in QT interval	n=84 adults; 74% m, mean age 63 y	HCQ+AZ Doses not specified	QT prolonged from baseline of 435 ± 24 ms to maximum 463 ± 32 ms (p<0.001) at day 3.6 ± 1.6 of treatment; 11% of patients developed severe QT prolongation >500 ms but no TdP events were recorded. Multivariate analysis identified development of acute renal failure, but not baseline QT, as a significant predictor of severe QT prolongation.

*Included 6 patients from their previously published study, described in the initial March 25, 2020 response.
**Same group as Gautret et al.
ARB=angiotensin II receptor blocker; AZ=azithromycin; CI=confidence interval; CT=computed tomography; f=female; HCQ=hydroxychloroquine; ICU=intensive care unit; m=male; MC=medical center; NS=not specified; NYU=New York University; OR=odds ratio; P=prospective; PNA=pneumonia; R=retrospective; TdP=Torsades de Pointes; TID=3 times daily; US=United States; VA=Veterans Affairs; y=years

References: 1. Molina JM et al. *Med Mal* 2020; In press. https://www.sciencedirect.com/science/article/pii/S0399077X20300858?via%3Dihub. 2. Gautret P et al. *Travel Med Infect Dis* 2020. Epub ahead of print. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7151271/. 3. Million M et al. Preprint. https://www.mediterranee-infection.com/early-treatment-of-1061-covid-19-patients-with-hydroxychloroquine-and-azithromycin-marseille-france/ 4. Magagnoli J et al. Preprint. https://www.medrxiv.org/content/10.1101/2020.04.16.20065920v2. 5. Chorin E et al. Preprint. https://www.medrxiv.org/content/10.1101/2020.04.02.20047050v1.