Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

International Journal of Infectious Diseases 99 (2020) 344–345

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Letter to the Editor

Possible synergistic effects of hydroxychloroquine and steroids in COVID-19, time for a nuanced approach. Comment on Arshad et al.

As its accompanying editorial (Lee et al., 2020) perceives, Arshad's report (Arshad et al., 2020) indeed fuels the fire of the hydroxychloroquine (HCQ) controversy. It also fans the steroid controversy (Salton et al., 2020).

The 2541 consecutive COVID-19 subjects included over seven weeks from 3/10/20 undoubtedly included 213 consecutive patients, starting on 3/12/20 for two weeks, in a pre/post quasi-experiment (Fadel et al., 2020). Fadel's conclusion that *"early short course of methylprednisolone* [MPD] *in . . . moderate to severe COVID-19 . . . improved clinical outcomes"* undoubtedly informed treatment protocols for the remaining five weeks of Arshad, affirming the editorial speculation that as the Henry Ford Hospital System *"became more experienced . . . , survival may have improved . . . "* With differences in steroid use noted in the editorial, a comparison with Fadel (Table 1) is intriguing:

1. *A similar "control" (~26%) mortality*
   (Row A) Late 70% HCQ use + late 57% steroid use, sicker (needing at least oxygen) patients
   = (Row C) No use HCQ + "mostly early" 36% steroid use, sicker plus less sick patients
2. *A similar treatment mortality (~13.5%):*
   (Row B) Early 79% HCQ use + early 68% steroid use, sicker patients
   = (Row D) Early 100% HCQ use + mostly early 79% steroid use, sicker plus less sick patients

With much lower HCQ usage, a similar pre/post study (Table 1 (Bani-Sadr et al., 2020)) found steroid-associated reduced mortality, but only after multivariate adjustment. These studies support the early combined in-hospital use of HCQ and MPD to reduce mortality and the need for ventilation. This contrasts with an effect of dexamethasone limited to more advanced disease (Horby et al., 2020), possibly reflecting between-steroid pharmacological differences (Draghici et al., 2020). Early use of MPD is supported by other studies, some of which (Salton et al., 2020) also involve HCQ with possible synergy via a lysosomal mechanism (He et al., 2011). HCQ, given alone at this stage, may require zinc (Carlucci et al., 2020). In Arshad's less sick and comorbid (propensity-matched) patients, HCQ's steroid requirement appears reduced. For early post-exposure prophylaxis in young subjects (Boulware et al., 2020; Wiseman et al., 2020), HCQ requires neither zinc nor steroid.

These data support prospective evaluation of a stage- and age-nuanced approach to COVID-19 that exploits the multiple mechanisms of HCQ and synergy with MPD. Detailed stratification of observational studies involving HCQ, steroids (and heparin) is urged, as well as the conduct of prospective meta-analyses of ongoing studies to facilitate meaningful sub-group analysis.

Table 1
Comparison of related studies involving hydroxychloroquine and steroids in COVID-19.

Row	Study	Group	Data type	n	HCQ Use%	Days	HCQ + AZI Use %	Steroid Use %	Days	Mortality % (HR)	HR. Cox
A	Fadel	Standard	Crude	81	70.4	3 (1–4)	in HCQ	Late 56.8	5 (3–7)	26.3	
B	Fadel	Steroid	Crude	132	78.8	1 (0–2)	in HCQ	Early 68.2	2 (1–3)	13.6 (0.52)	
C	Arshad	None	Crude	409	0	NA	0	35.7	NA	26.4	
D	Arshad	HCQ	Crude	1202	100	1 (1–2)	0	78.9	NK	13.5 (0.51)	0.34
E	Arshad	None/AZI	Propensity	190			0	44.2	NK	NK	–
F	Arshad	HCQ + AZI	Propensity	190			100	44.2	NK	NK	0.487
G	Arshad	AZI	Crude	147	0	NK	100	38.8	NK	22.4 (0.85)	1.05
H	Arshad	HCQ/AZI (severe)	Crude	783	100	NK	100	74.3	NK	20.1 (0.76)	0.294
I	Bani-Sadr	Standard	Crude	85	13.3	NK	0	12.9	At SOB	20	–
J	Bani-Sadr	Steroid	Crude	172	6	NK	0	69.2	At SOB	18 (0.9)	0.47

NK, Not known (information not supplied in paper).
Days, Median days (IQR) to drug use.

http://dx.doi.org/10.1016/j.ijid.2020.07.064

Funding source

This work has not been funded by any entity. The author declares that he and Synechion, Inc., have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical approval

Ethical approval was not required for this letter.

References

Arshad S, Kilgore P, Chaudhry ZS, et al. Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. Int J Infect Dis 2020;, doi:http://dx.doi.org/10.1016/j.ijid.2020.06.099 Epub 2020 July 1.

Bani-Sadr F, Hentzien M, Pascard M, et al. Corticosteroid therapy for patients with CoVID-19 pneumonia: a before-after study. Int J Antimicrob Agents 2020;106077, doi:http://dx.doi.org/10.1016/j.ijantimicag.2020.106077 Epub 2020 July 8.

Boulware DR, Pullen MF, Bangdiwala AS, et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. N Engl J Med 2020;, doi:http://dx.doi.org/10.1056/NEJMoa2016638 Epub 2020 June 4.

Carlucci P, Ahuja T, Petrilli CM, et al. Hydroxychloroquine and azithromycin plus zinc vs. hydroxychloroquine and azithromycin alone: outcomes in hospitalized COVID-19 patients. medRxiv 2020;, doi:http://dx.doi.org/10.1101/2020.05.02.20080036.

Draghici S, Nguyen T-M, Sonna LA, et al. COVID-19: disease pathways and gene expression changes predict methylprednisolone can improve outcome in severe cases. medRxiv 2020;, doi:http://dx.doi.org/10.1101/2020.05.06.20076687.

Fadel R, Morrison AR, Vahia A, et al. Early short course corticosteroids in hospitalized patients with COVID-19. Clin Infect Dis 2020;, doi:http://dx.doi.org/10.1093/cid/ciaa601 Epub 2020 May 20.

He Y, Xu Y, Zhang C, et al. Identification of a lysosomal pathway that modulates glucocorticoid signaling and the inflammatory response. Sci Signal 2011;4:ra44, doi:http://dx.doi.org/10.1126/scisignal.2001450.

Horby P, Lim WS, Emberson J, et al. Effect of dexamethasone in hospitalized patients with COVID-19: preliminary report. medRxiv 2020;, doi:http://dx.doi.org/10.1101/2020.06.22.20137273.

Lee TC, MacKenzie LJ, McDonald EG, et al. An observational cohort study of hydroxychloroquine and azithromycin for COVID-19: (can't get no) satisfaction. Int J Infect Dis 2020;, doi:http://dx.doi.org/10.1016/j.ijid.2020.06.095 Epub 2020 July 2.

Salton F, Confalonieri P, Santus P, et al. Prolonged low-dose methylprednisolone in patients with severe COVID-19 pneumonia. medRxiv 2020;, doi:http://dx.doi.org/10.1101/2020.06.17.20134031.

Wiseman DM, Kory P, Mazzucco D, Ramesh MS. Preventing disease after exposure to COVID-19 using hydroxychloroquine: A summary of a protocol for exploratory re-analysis of age and time-nuanced effects. medrxiv 2020;, doi:http://dx.doi.org/10.1101/2020.08.19.20178376.

David M. Wiseman PhD MRPharmS
Synechion, Inc., 18208 Preston Road, Suite D9-405, Dallas, TX 75252, United States
E-mail address: synechion@aol.com (D. Wiseman).

Received 8 July 2020