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.

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Letter to the Editor

More gastro-intestinal adverse events in non-ICU hospitalised COVID-19 patients treated with chloroquine versus hydroxychloroquine

With great interest we read the observational cohort study of Lammers and colleagues, in which they investigated the effect of hydroxychloroquine and chloroquine in non-ICU hospitalized COVID-19 patients. They found that early treatment with hydroxychloroquine was associated with a reduced risk of transfer to the ICU, whereas chloroquine did not reduce this risk. A possible explanation for the observed difference of hydroxychloroquine as compared to chloroquine might be a better safety profile of hydroxychloroquine (Liu et al., 2020; Pereira, 2020; Yao et al., 2020).

Known adverse events in hydroxychloroquine and chloroquine are neurotoxicity, cardiotoxicity and gastro-intestinal symptoms. We conducted an observational cohort study, comparing gastro-intestinal adverse events in non-ICU hospitalized COVID-19 patients treated with chloroquine versus hydroxychloroquine. The study population consisted of all patients $\geq$ 18 years with proven COVID-19 of moderate severity, hospitalized in a non-ICU setting in Radboudumc or Rijnstate Hospital and treated with hydroxychloroquine (Rijnstate Hospital) or chloroquine (Radboud University Medical Center) between March 3, 2020 and May 1, 2020. The primary outcome was discontinuation of treatment course due to gastro-intestinal adverse events (diarrhea, nausea, abdominal pain, newly developed after start of treatment course). The analysis included multivariable logistic regression corrected for age (the two cohorts were relatively homogeneous except for the factor of age).

A total of 246 patients were included in the study, with 166 patients in the hydroxychloroquine group and 80 patients in the chloroquine group. In the hydroxychloroquine group 1.3% of the patients discontinued the treatment course due to gastro-intestinal adverse events, compared to 17% in the chloroquine group ($p < 0.001$; OR 17 [95% CI 3.4–80]). The incidence of gastro-intestinal adverse events was significantly higher in the chloroquine group (40%) compared to the hydroxychloroquine group (18%) ($p < 0.001$; OR 3.0 [95%CI 1.6–5.6]) (Table 1). These findings suggest that treatment with chloroquine was associated with an increased risk for gastro-intestinal adverse events, which subsequently led to an increased risk for discontinuing treatment, compared to hydroxychloroquine.

This study shows that, over short term use, chloroquine causes more gastro-intestinal adverse events than hydroxychloroquine at dosages given for COVID-19. When considering the outcome of the study of Lammers et al., the observed difference in risk for transfer to the ICU between patients treated with hydroxychloroquine versus chloroquine could be partially explained by the observed difference in gastro-intestinal adverse events.

Table 1
Gastro-intestinal adverse events by treatment group.

	No./Total No. (%)			
	Hydroxychloroquine (n = 166)	Chloroquine (n = 80)	Adjusted p-value[a]	Adjusted OR[a] (95% CI)
Completeness of treatment course (n = 149 and n = 79)				
Completed treatment course	123/149 (83)	46/79 (58)	<0.001*	
Discontinued treatment course	26/149 (17)	33/79 (42)	<0.001*	
Due to gastro-intestinal adverse events	2/149 (1.3)	13/79 (17)	<0.001*	17 (3.4–80)*
- Nausea/vomiting	2/149 (1.3)	8/79 (10)	0.009*	9.0 (1.7–47)*
- Diarrhea	0/149 (0.0)	5/79 (6.3)	NA[b]	NA[b]
- Abdominal pain	0/149 (0.0)	0/79 (0.0)	NA[b]	NA[b]
Gastro-intestinal adverse events	30/166 (18)	32/80 (40)	<0.001*	3.0 (1.6–5.6)*
- Nausea/vomiting	18/166 (11)	18/80 (23)	0.013*	2.6 (1.2–5.4)*
- Diarrhea	13/166 (7.8)	20/80 (25)	0.001*	3.6 (1.7–7.8)*
- Abdominal pain	6/166 (3.6)	0/80 (0.0)	NA[b]	NA[b]
Requirement for comedication duringtreatment				
Start of antiemetics during treatment	20/166 (12)	13/80 (16)	0.354	1.5 (0.7–3.2)
- Metoclopramide	19/166 (11)	12/80 (15)		
- Other	3/166 (1.8)	1/80 (1.3)		
Start of loperamide during treatment	1/166 (0.6)	5/80 (6.3)	0.029*	11 (1.3–103)*

* Statistically significant (p-value <0.05).
[a] Tested with multivariable logistic regression adjusted for age categories.
[b] Not available (NA), logistic regression test not possible due to zero frequencies.

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Conflict of interest

None.

Ethical approval

The study was approved by the ethical committee of the Radboudumc, the Netherlands (CMO: 2020-6526).

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