Viral respiratory infections in patients treated with hydroxychloroquine

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Chloroquine (CQ) and hydroxychloroquine (HCQ) have been shown to have anti-viral effect in in-vitro studies on a range of viruses, including SARS-CoV-2 (1, 2). CQ and HCQ are classified as disease-modifying anti-rheumatic drugs (DMARD) and they are used in the treatment of several rheumatic diseases (3, 4). Whether these drugs have an inhibitory effect on viral infections in real-life cohorts is not known (5). The NOR-DMARD is a multi-centre longitudinal study, established in 2000, that prospectively records disease activity in patients with inflammatory joint disease (IJD) starting treatment with DMARDs. Composite scores of disease activity including the disease activity score for 28 joints (DAS-28) are calculated at baseline, three months and every 6 months thereafter (6).

We have recently compared the rates of viral respiratory infections between patients with IJD who have received HCQ and patients who have received comparable DMARDS, but not HCQ.

In these analyses we defined baseline as the first visit where use of HCQ, methotrexate or sulfasalazine was registered either as a monotherapy or as a co-medication in the period 2006-2018. End of follow-up was the last visit registered, death or censor. The NOR-DMARD has been linked to three Norwegian national registers that record diagnoses given by the primary and secondary health care services, and death. A combined primary outcome of influenza and/or viral pneumonia was constructed (ICD10 J10, J11, J12 and/or ICPC-2 R78, R80). The study was approved by the Ethical Committee of South-Eastern Norway.

We estimated a propensity score from a logistical model examining predictors for HCQ use, and each patient on HCQ was matched to up to 5 comparators according to the propensity score. Baseline variables were compared using Student t-test, Mann-Whitney U-test and χ^2 as appropriate. Incidence rate per 1000 PYR were calculated and 95% CI estimated according to the Poisson distribution. Cox-regression models adjusted for age and gender were constructed and possible confounding was explored.

Five hundred and two patients on HCQ were matched to 2409 comparators according to the propensity score. Table I presents baseline and outcome variables for the propensity matched cohort. There were a total of 6525 years at risk and 335 primary outcomes observed. Use of HCQ did not predict the occurrence of respiratory viral infection, hazard ratio (HR (95% CI) 0.93 (0.67–1.28)). When work disability/pension was added to the model, the HR for use of HCQ *versus* comparators increased to 1.19 (0.36–4.02). There were no other confounders of the model.

Table I. Comparison of baseline and outcome variables between patients treated with hydroxychloroquine and comparators in the propensity matched cohort.

	Hydroxychloroquine treated	Non-hydroxy-chloroquine	*p*-value
Demographics	502	2409	
Age years median (IQR)	55.9 (46.0-63.7)	56.5 (45.7-65.4)	0.33
Female gender n (%)	392 (78.1)	1879 (78.0)	0.97
Diagnosis			
RA n (%)	395 (78.7)	1849 (76.8)	0.35
Disease duration median (IQR)	6.3 (2.1-15.9)	5.2 (0.7-14.2)	0.001
Work disabled/retired	43 (55.1)	141 (45.9)	0.15
Baseline variables			
CRP mg/L	13.0 (18.8)	13.2 (19.3)	0.73
ESR	22.1 (0.9)	22.4 (0.4)	0.93
DAS28	4.1 (1.5)	4.1 (1.5)	0.87
CDAI	17.2 (11.2)	17.4 (12.4)	0.76
Treatment			
Sulfasalazine	203 (40.4)	408 (16.9)	<0.001
Methotrexate n (%)	379 (75.5)	2142 (88.9)	<0.001
Biologics n (%)	219 (43.6)	1077 (44.7)	0.66
Respiratory viral infections			
Number with primary event	43 (8.6)	292 (12.1)	0.02
Previous resp. viral infection	90 (17.9)	385 (16.0)	0.28
Patient years at risk			
Patient years at risk	860.5	5664.0	
IR/1000 PYR	50.0	51.6	
IRR (95% CI)	1.0 (0.7-1.3)		0.86
Propensity score (SD)	0.07 (0.2)	0.07 (0.02)	0.39

Baseline variables were compared using Student t-test, Mann-Whitney U-test and χ^2 as appropriate.
Incidence rate per 1000 PYR were calculated and 95% CI estimated according to the Poisson distribution.
IQR: (inter-quartile range); n: number, RA: rheumatoid arthritis; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; DAS28: disease activity score for 28 joints; CDAI: Clinical Disease Activity Index; IRR: incidence rate ratio; PYR: patient years at risk; Number: number of patients with available data.

We found no evidence that use of HCQ prevented the development of viral respiratory infections in this real-life prospective longitudinal observational study. Our study supports the conclusion of a randomised controlled trial which reported that use of CQ did not prevent influenza in adults (7), and we believe that data from real-life heterogeneous cohorts are important supplements. Recently a large randomised controlled trial has concluded that there is no evidence for the prophylactic effect of HCQ in patients infected with SARS-CoV-2.

The majority of cases reported in this study are from diagnoses reported by general practitioners and unfortunately there is no information regarding the type of virus. Patients may also have chosen not to contact the health services. The propensity model matched for a number of possible confounding factors, but residual confounding is also limitation as illustrated by work disability acting as a confounder to the model. Another weakness is the lack information concerning vaccination status. In Norway, vaccination for seasonal influenza is recommended to patients on biologics and/or above 65 years of age.

We conclude that there was no evidence that use of HCQ prevented viral respiratory infections.

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