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Corticosteroid therapy is associated with the delay of SARS-CoV-2 clearance in COVID-19 patients

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ABSTRACT

The impact of corticosteroid treatment on virological course of coronavirus disease 2019 (COVID-19) patients remains unclear. This study aimed to explore the association between corticosteroid and viral clearance in COVID-19. The clinical data of COVID-19 patients from 10 hospitals of Jiangsu, China, were retrospectively collected. Cox regression and Kaplan–Meier analysis were used to analyze the adverse factors of virus clearance. Of the 309 COVID-19 patients, eighty-nine (28.8%) patients received corticosteroid treatment during hospitalization. Corticosteroid group showed higher C-reactive protein (median 11.1 vs. 7.0 mg/l, $P = 0.018$) and lower lymphocytes (median 0.9 vs. 1.4 $\times 10^9$/l, $P < 0.001$) on admission. Fever (93.3% vs. 65.0%, $P < 0.001$) and cough (69.7% vs. 57.3%, $P = 0.043$) were more common in corticosteroid group. The proportions of patients with severe illness (34.8% vs. 1.8%, $P < 0.001$), respiratory failure (25.8% vs. 1.4%, $P < 0.001$), acute respiratory distress syndrome (4.5% vs. 0%, $P = 0.002$), and admission to ICU (20.2% vs. 0.9%, $P < 0.001$) were significantly higher in corticosteroid group than non-corticosteroid group. The duration of virus clearance (median 18.0 vs. 16.0 days, $P < 0.001$) and hospitalization (median 17.0 vs. 15.0 days, $P < 0.001$) were also significantly longer in corticosteroid group than non-corticosteroid group. Treated with corticosteroid (Hazard ratio [HR], 0.698; 95% confidence interval [CI], 0.512 to 0.951; $P = 0.023$) was an adverse factor of the clearance of SARS-CoV-2, especially for male patients (HR, 0.620; 95% CI, 0.408 to 0.942; $P = 0.025$). The

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cumulative probability of SARS-CoV-2 clearance was lower in corticosteroid group ($P < 0.001$). Corticosteroid treatment may delay the SARS-CoV-2 clearance of COVID-19 patients and should be used with cautions.

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), rapidly spread around the world (Chen et al., 2020; Huang et al., 2020; Zhu et al., 2020). As of August 16, 2020, 21,294,845 cases of COVID-19 had been reported in the world, and 761,779 patients were died (World Health Organization, 2020). The clinical spectrum of COVID-19 ranges from asymptomatic to critically ill with fatal outcomes (Goyal et al., 2020; Guan et al., 2020). The mortality rate in COVID-19 patients with critically ill was ranged from 26% to 61.5%.

Several studies have demonstrated that cytokine storm was associated with the severity and clinical outcomes of COVID-19 patients (Ma et al., 2020; Mehta et al., 2020; Ye et al., 2020). Corticosteroids were reported to have possible benefit by reducing inflammation-induced lung injury by suppressing lung inflammation (Huang et al., 2020). Corticosteroids have been used for the treatment of COVID-19 patients, especially in the critically ill cases (Guan et al., 2020; Yang et al., 2020). The expert consensus statement by Chinese Thoracic Society recommended the using corticosteroids prudently of short courses at low-to-moderate dose for critically ill COVID-19 patients (Shang et al., 2020). However, several studies have reported that corticosteroid therapy was associated with the delay of SARS-CoV-2 viral clearance (Zha et al., 2020). Thus, the clinical benefit of corticosteroid therapy for COVID-19 patients remains controversial (Fang et al., 2020; Zha et al., 2020). In this retrospective, multi-center study, we investigated the impact of corticosteroid therapy on the viral clearance of SARS-CoV-2 in COVID-19 patients.

2. Materials and methods

2.1. Patients

Three hundred and forty-two patients with COVID-19 who were admitted in 10 designated hospitals of Jiangsu province, China from January 18, 2020 to February 26, 2020 were included in the present study. All confirmed patients were tested positive for SARS-CoV-2 in local Center for Disease Control using reverse transcription polymerase chain reaction (RT-PCR) method based on previous report (World Health Organization, 2020). The clinical outcomes of patients were followed up to February 29, 2020. The study was approved by Ethics Committee of these hospitals, with a waiver of informed consent.

2.2. Data collection and definitions

Demographic and clinical information was retrospectively collected from electronic medical records. All data was entered in computerized database for further analysis.

Respiratory failure and acute respiratory distress syndrome (ARDS) were diagnosed based on the corresponding guidelines (ARDS Definition Task Force et al., 2012). The criteria of discharge was according to the guideline by the Chinese National Health Commission (National Health Commission, 2020). The viral clearance was defined as two consecutively negative SARS-CoV-2 nucleic acid by RT-PCR test with separated by at least 1 day. The time of negative PCR was calculated from the onset of symptoms to the date of the second negative RT-PCR test.

2.3. Statistical analysis

Continuous variables were presented as medians (interquartile range (IQR)), while categorical variables were presented as the counts and percentages. The independent group t tests (normal distribution) or Mann-Whitney U (non-normal distribution) were used to compared continuous variables between groups. Chi-square or Fisher exact test was used to compare the categorical variables. Cox regression analysis was used to analyze the risk factors of long virus clearance duration. Variables having P values < 0.1 in the univariate analysis were further used for a multivariate Cox regression analysis. The cumulative incidences of viral clearance were estimated by the Kaplan-Meier method. $P < 0.05$ was regards as statistical significant. SPSS version 22.0 software (SPSS Inc. Chicago, IL, United States) was used for the data analysis.

3. Results

3.1. Demographic and clinical characteristics

Of the 342 COVID-19 patients, 14 patients with insufficient data were excluded. Given that the viral shedding could not be defined, nineteen asymptomatic patients were also excluded. Eventually, 309 patients were enrolled in this study. The median age of patients was 45.0 (IQR 33.0–55.0) years and about half (54.0%) of the patients were male. Forty-eight (15.5%) patients had a history of hypertension and 25 (8.1%) patients had type 2 diabetes on admission. The most common symptoms were fever (73.1%) and cough (60.8%). The median levels of white blood cells (WBC), lymphocytes, alanine transaminase (ALT), creatinine (Cr), prothrombin time (PT), and C-reactive protein (CRP) were 4.8 (IQR 3.8–6.1) $\times 10^9$/l, 1.2 (IQR 0.9–1.6) $\times 10^9$/l, 26.0 (IQR 19.0–37.0) U/L, 64.0 (IQR 52.0–78.0) μmol/l, 12.8 (IQR 12.0–13.4) s, and 8.3 (IQR 2.3–21.1) mg/l. The majority patients (93.2%) had abnormal chest CT images on admission. The median time from symptom onset to admission was 5.0 (IQR 2.0–8.0) days (Table 1).

During hospitalization, at least one dose of corticosteroid was administered to 89 (28.8%) patients. All patients received low-dose of corticosteroid treatment (40–160 mg/d methylprednisolone). Patients who received corticosteroid treatment were older (median 48.0 vs. 41.0 years, $P = 0.018$) and male dominate (64.0% vs. 50.0%, $P = 0.025$) than patients without corticosteroid treatment. More patients in corticosteroid group had type 2 diabetes than non-corticosteroid group (16.9% vs. 4.5%, $P < 0.001$). More patients had fever (93.3% vs. 65.0%, $P < 0.001$) and cough (69.7% vs. 57.3%, $P = 0.043$) in patients with corticosteroid treatment than patients without corticosteroid treatment. The lymphocyte counts (median 0.9 vs. 1.4 $\times 10^9$/l, $P < 0.001$) in patients with corticosteroid treatment was significantly lower than patients without corticosteroid, while CRP level (median 11.1 vs. 7.0 mg/l, $P = 0.018$) in patients with corticosteroid treatment was significantly higher than patients without corticosteroid treatment. The proportion of abnormal chest CT images was higher in patients with corticosteroid treatment than patients without corticosteroid treatment (98.9% vs. 90.9%, $P = 0.012$) (Table 1).

3.2. Treatment and clinical outcomes

The proportions of patients treated with atomized inhalation of interferon α-2b, lopinavir-ritonavir, and arbidol were 57.9%, 74.8%, and 46.0, respectively. As of February 29, 2020, 26 (8.4%) patients developed respiratory failure and 4 (1.3%) patients progressed to ARDS. Thirty-five (11.3%) patients had severe illness and 20 (6.5%) patients were transferred to the intensive care unit (ICU) during hospitalization. As of February 29, 2020, 275 (89.0%) patients developed virus clearance and the median days of SARS-CoV-2 negativity after symptom onset were 17.0 (IQR 13.0–20.0) days. Two hundred and thirty-six

Table 1
Clinical characteristics of COVID-19 patients.

Variables (n [%] or median [IQR])	All patients (n = 309)	Non-corticosteroid (n = 220)	Corticosteroid (n = 89)	p value
Age (yryr)	45.0 (33.0, 55.0)	41.0 (32.0, 54.0)	48.0 (36.0, 57.0)	0.018
Male	167 (54.0)	110 (50.0)	57 (64.0)	0.025
Comorbidities				
Hypertension	48 (15.5)	31 (14.1)	17 (19.1)	0.271
Type 2 diabetes	25 (8.1)	10 (4.5)	15 (16.9)	<0.001
Onset signs and symptoms				
Fever	226 (73.1)	143 (65.0)	83 (93.3)	<0.001
Cough	188 (60.8)	126 (57.3)	62 (69.7)	0.043
Fatigue	68 (22.0)	44 (20.0)	24 (27.0)	0.181
Sore throat	34 (11.0)	20 (9.1)	14 (15.7)	0.091
Muscle ache	35 (11.3)	26 (11.8)	9 (10.1)	0.668
Headache	20 (6.5)	18 (8.2)	2 (2.2)	0.055
Days from symptom onset to admission	5.0 (2.0, 8.0)	5.0 (2.0, 8.0)	5.0 (3.0, 8.0)	0.375
Laboratory and imaging findings				
WBC ($\times 10^9$/l)	4.8 (3.8, 6.1)	4.8 (3.8, 6.1)	4.9 (3.7, 6.1)	0.554
Lymphocyte ($\times 10^9$/l)	1.2 (0.9, 1.6)	1.4 (1.0, 1.7)	0.9 (0.7, 1.2)	<0.001
ALT (U/L)	26.0 (19.0, 37.0)	25.0 (18.0, 37.0)	27.0 (21.9, 40.0)	0.05
Cr (μmol/l)	64.0 (52.0, 78.0)	62.8 (50.1, 76.0)	68.8 (56.5, 85.7)	0.004
PT (s)	12.8 (12.0, 13.4)	12.8 (12.1, 13.5)	12.9 (12.0, 13.3)	0.602
CRP (mg/l)	8.3 (2.3, 21.1)	7.0 (1.7, 18.9)	11.1 (4.1, 26.6)	0.018
Chest CT				
No pneumonia	21 (6.8)	20 (9.1)	1 (1.1)	0.012
Unilateral pneumonia	45 (14.6)	37 (16.8)	8 (9.0)	0.077
Bilateral pneumonia	243 (78.6)	163 (74.1)	80 (90.0)	0.002

IQR, interquartile range; WBC, white blood cells; ALT, alanine transaminase; Cr, creatinine; PT, prothrombin time; CRP, C-reactive protein.

(76.4%) patients were discharged up to February 29, 2020. However, no patient died in our study (Table 2).

More patients were treated with lopinavir-ritonavir in corticosteroid group than non-corticosteroid group (89.9% vs.68.6%, P < 0.001), while there were no significant differences in the proportion of patients who received atomized inhalation of interferon α-2b and arbidol between two groups. Regarding complications and outcomes, more patients developed respiratory failure (25.8% vs. 1.4%, P < 0.001) and ARDS (4.5% vs. 0%, P = 0.002) in patients with corticosteroid treatment. The proportion of patients with severe illness (34.8% vs. 1.8%, P < 0.001) and admission to ICU in corticosteroid treatment group (20.2% vs. 0.9%, P < 0.001) was also significantly higher than non-corticosteroid group. The median days of SARS-CoV-2 negativity after symptom onset (18.0 vs. 16.0 days, P < 0.001) and hospitalization (17.0 vs. 15.0 days, P < 0.001) in corticosteroid group were significantly longer than non-corticosteroid group. (Table 2). The proportion of corticosteroid treatment in patients with severe illness (88.6%) was significantly higher than in patients with mild illness (21.2%, P < 0.001).

Table 2
Treatment, complications, and outcomes of COVID-19 patients.

Variables (n [%] or median [IQR])	All patients (n = 309)	Non-corticosteroid (n = 220)	Corticosteroid (n = 89)	P value
Drug treatment				
Atomized inhalation of interferon α-2b	179 (57.9)	120 (54.5)	59 (66.3)	0.058
Lopinavir-ritonavir	231 (74.8)	151 (68.6)	80 (89.9)	<0.001
Arbidol	142 (46.0)	99 (45.0)	43 (48.3)	0.597
Complications				
Respiratory failure	26 (8.4)	3 (1.4)	23 (25.8)	<0.001
ARDS	4 (1.3)	0	4 (4.5)	0.002
Outcomes				
Severe illness	35 (11.3)	4 (1.8)	31 (34.8)	<0.001
Admission to ICU	20 (6.5)	2 (0.9)	18 (20.2)	<0.001
Death	0	0	0	–
Day of negative PCR from symptom onset	17.0 (13.0, 20.0)	16.0 (13.0, 19.0)	18.0 (15.0, 23.0)	<0.001
Discharged	236 (76.4)	167 (75.9)	69 (77.5)	0.762
Day of hospitalization (days)	15.0 (12.0, 20.0)	15.0 (12.0, 19.0)	17.0 (14.0, 23.0)	<0.001

IQR, interquartile range; ICU, Intensive care unit; PCR, polymerase chain reaction.

3.3. The adverse factors of the clearance of SARS-CoV-2

Univariate Cox regression analysis presented that age >60 years (hazard ratio [HR], 0.464; 95% confidence interval [CI], 0.319 to 0.674; P < 0.001), concurrent hypertension (HR, 0.595; 95% CI, 0.420 to 0.843; P = 0.004), type 2 diabetes (HR, 0.644; 95% CI, 0.411 to 1.008; P = 0.004), severe illness (HR, 0.604; 95% CI, 0.415 to 0.881; P = 0.009), admission to ICU (HR, 0.607; 95% CI, 0.374 to 0.983; P = 0.043), and treated with corticosteroid (HR, 0.644; 95% CI, 0.493 to 0.840; P = 0.001) were associated with the clearance of SARS-CoV-2. Further multivariate analysis showed age >60 years (HR, 0.543; 95% CI, 0.366 to 0.805; P = 0.002) and treated with corticosteroid (HR, 0.698; 95% CI, 0.512 to 0.951; P = 0.023) were independent adverse factors of SARS-CoV-2 clearance. However, the severe illness was not associated with SARS-CoV-2 clearance (HR, 0.680; 95%CI 0.392 to 1.180; P = 0.171) (Table 3). During the study period, the cumulative probability of SARS-CoV-2 clearance was significantly lower in corticosteroid group compared to non-corticosteroid group, with 15-day cumulative incidences of 27.2% and 44.2%, 30-day cumulative incidences of 87.9% and 95.8%, respectively (Log Rank $\chi^2 = 11.97$, P < 0.001) (Fig. 1A).

Further subgroup analysis was performed according to gender of COVID-19 patients. For male patients, age >60 years (HR, 0.480; 95% CI, 0.265 to 0.869; P = 0.015) and treated with corticosteroid (HR, 0.620; 95% CI, 0.408 to 0.942; P = 0.025) were independent adverse factors for SARS-CoV-2 clearance (Supplemental table 1). The cumulative probability of SARS-CoV-2 clearance for male patients was significantly lower in corticosteroid group than non-corticosteroid group, with 15-day cumulative incidences of 22.8% and 43.4%, 30-day cumulative incidences of 86.0% and 96.9%, respectively (Log Rank $\chi^2 = 8.897$, P = 0.003) (Fig. 1B). The results were similar with entire patients. However, for female patients, treated with corticosteroid (HR, 0.714; 95% CI, 0.464 to 1.098; P = 0.125) was not associated with SARS-CoV-2 clearance (Supplemental table 2). The cumulative probability of SARS-CoV-2 clearance for female patients was comparable between corticosteroid group and non-corticosteroid group (Log Rank $\chi^2 = 2.649$, P = 0.104) (Fig. 1C).

Table 3
Cox regression analysis of factors for the clearance of SARS-CoV-2.

Variables	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (yr)				
≤60	Reference			
>60	0.464 (0.319, 0.674)	<0.001	0.543 (0.366, 0.806)	0.002
Sex				
Female	Reference			
Male	0.897 (0.706, 1.140)	0.376		
Hypertension				
No	Reference			
Yes	0.595 (0.420, 0.843)	0.004	0.727 (0.504, 1.049)	0.088
Type 2 diabetes				
No	Reference			
Yes	0.644 (0.411, 1.008)	0.054	0.965 (0.599, 1.553)	0.882
WBC				
No decreased	Reference			
Decreased	1.167 (0.895, 1.521)	0.255		
Lymphocyte				
No decreased	Reference			
Decreased	0.884 (0.683, 1.145)	0.35		
Severe illness				
No	Reference			
Yes	0.604 (0.415, 0.881)	0.009	0.680 (0.392, 1.180)	0.171
ICU admission				
No				
Yes	0.607 (0.374, 0.983)	0.043	1.125 (0.584, 2.168)	0.724
Glucocorticoid				
No	Reference			
Yes	0.644 (0.493, 0.840)	0.001	0.698 (0.512, 0.951)	0.023

WBC, white blood cells; ICU, Intensive care unit; HR, hazard ratio; CI, confidence interval.

4. Discussion

During the outbreaks of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), corticosteroids were widely used (Stockman et al., 2006). Corticosteroids were reported to play a role in suppressing lung inflammation. However, corticosteroid treatment may also inhibit the immune responses and pathogen clearance (Russell et al., 2020). It was reported that corticosteroid treatment did not improve the clinical outcomes of SARS and MERS, but delayed the viral clearance (Auyeung et al., 2005; Hui, 2018).

Corticosteroids are widely used in the treatment of COVID-19 patients in addition to other therapeutics. It was reported that 18.6%–44.9% of the COVID-19 patients received corticosteroid treatment (Guan et al., 2020; Wang et al., 2020). In our study, 89 (28.8%) of 309 patients were treated with corticosteroids. Patients who treated with corticosteroids had more clinical symptoms such as fever, cough, and more abnormalities of chest CT images on admission. More patients with corticosteroid treatment had respiratory failure and ARDS. The proportions of patients with severe illness and admission to ICU were also higher in corticosteroid group. In patients with severe illness, the proportion of corticosteroid treatment (88.6%) was significantly higher than in patients with mild illness (21.2%), which was similar to the previous studies (Huang et al., 2020; Zha et al., 2020). Our study indicated that more patients with severe illness of COVID-19 were likely to receive corticosteroid treatment.

The clinical benefits of corticosteroid treatment for patients with COVID-19 remains controversial. Zha et al. assessed the efficacy of corticosteroid treatment in 31 COVID-19 patients (Zha et al., 2020). They found that corticosteroid treatment did not impact the virus clearance time and hospital length of stay (Zha et al., 2020). However, the sample size is very small. Fang et al. investigated the effect of low-dose corticosteroid therapy on SARS-CoV-2 clearance time, which indicating that corticosteroid therapy may not delay viral clearance (Fang et al., 2020). Xu et al. found that corticosteroid treatment was associated with prolonged viral RNA shedding time in COVID-19 patients and COVID-19 patients with early RNA clearance (<16 days) had lower proportion of patients using corticosteroid treatment than patients with late RNA clearance (Xu et al., 2020). However, in that report, the corticosteroid usage was not independently related to the prolonged viral RNA shedding in the multivariable model (Xu et al., 2020). In the present study, corticosteroid treatment was independently associated with delay of SARS-CoV-2 viral clearance after adjusting for the confounding factors. The cumulative probability of SARS-CoV-2 clearance was also significantly lower in corticosteroid group. In addition, increasing evidences suggested that male COVID-19 patients had more severe clinical outcomes than female patients (Guan et al., 2020; Yang et al., 2020). The potential cause may be explained that the expression of angiotensin converting enzyme receptor (ACE2) was more predominant in men than in women (Zhao et al., 2020), which is an essential molecule for SARS-CoV-2 virus entry into target cells (Bourgonje et al., 2020). Therefore, we further compared the impact of corticosteroid on SARS-CoV-2 viral clearance between male patients and female patients. The results revealed that treated with corticosteroid resulted in the delay of SARS-CoV-2 viral clearance in male patients, while corticosteroid did not affect SARS-CoV-2 viral clearance in female patients. Previous study demonstrated that the corticosteroid receptor gene expression levels were higher in male than in female, which may be a significant reason causing the result (O'Connor et al., 2013). Thus, our results indicated that corticosteroid therapy was associated with the delay of SARS-CoV-2 clearance in COVID-19 patients, especially for male patients.

This study had some limitations. First, the patients were retrospectively included. Thus, many confounders may have influenced our results. Second, a controlled, open-label study from United Kingdom demonstrated that use of corticosteroid could reduce the 28-day mortality in a large COVID-19 cohort (Horby et al., 2020). However, the case fatality rate was incredible high (>20%) in that study (Horby et al., 2020). In contrast, the COVID-19 patients had less severe disease with no patient deceased in our study. Thus, the clinical benefits of corticosteroid treatment in COVID-19 patients with different severity and

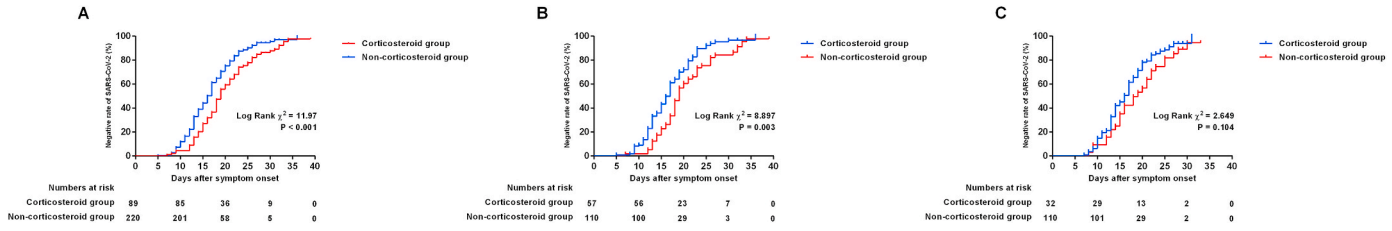

Fig. 1. The cumulative incidence of SARS-CoV-2 clearance in the corticosteroid group and non-corticosteroid group (A, entire patients; B, male patients; C, female patients).

ethnicities deserve further investigation.

In conclusion, corticosteroid treatment may delay clearance of SARS-CoV-2 in COVID-19 patients, especially for male patients. Thus, corticosteroids should be used with cautions. However, more randomized controlled trials are required to investigate the clinical benefits of corticosteroid treatment for COVID-19.

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CRediT authorship contribution statement

Concept and design: Chao Wu, Longgen Liu and Xuebing Yan. Drafting of the manuscript: Rui Huang, Chuanwu Zhu, Jian Wang, Leyang Xue, Chunyang Li Xiaomin Yan; Critical revision of the manuscript for important intellectual content: Yuxin Chen, Chuanwu Zhu, Longgen Liu and Xuebing Yan. Statistical analysis: Jian Wang, Rui Huang. Administrative, technical, or material support: Longgen Liu, Haiyan Zhao. Supervision: Chao Wu, Longgen Liu and Xuebing Yan. Acquisition, analysis, or interpretation of data: Rui Huang, Jian Wang, Songping Huang, Jie Wei, Xiaomin Yan, Xiang-an Zhao, Fang Ming, Li Zhu, Biao Zhang, Leyang Xue, Shuqin Hong, Tianmin Xu, Chunyang Li, Xuebing Yan, Yun Zhao, Juan Cheng, Dawen Sang, Huaping Shao, Rahma Issa, Haiyan Zhao, Xinying Guan and Xiaobing Chen. All authors reviewed and approved the final version.

Declaration of competing interest

The authors have declared that no conflicts of interest exist.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejphar.2020.173556.

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