Review

High-dose glucocorticoids pulse-therapy for beta-coronaviridae pneumonia: a systematic literature review and case-series of Coronavirus disease-2019

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ABSTRACT

Objective. *The results of the RECOVERY trial identified dexamethasone as the first pharmacological therapy that reduces mortality in patients with COVID-19. The aim of this paper is to conduct a systematic literature review on safety and efficacy of pulse glucocorticoid therapy for Severe Acute Respiratory Syndrome (SARS)-CoronaVirus (CoV), Middle East Respiratory Syndrome (MERS)-CoV or SARS-CoV-2 infections and describe a case-series of COVID-19 patients treated with off-label pulse doses of methylprednisolone.*

Methods. *We performed a systematic literature review on safety and efficacy of pulse therapy for betacoronaviridae infections as described in the protocol registered on PROSPERO (CRD42020190183). All consecutive patients admitted to Arcispedale Santa Maria Nuova di Reggio Emilia or Guastalla Hospital with COVID-19 between March 1st and April 30th 2020 and treated with methylprednisolone 1 gram/day for at least three days were included in the case series. A retrospective review of available computed tomography (CT) scan and chest x-ray was performed independently by two radiologists blinded to clinical data, and discordances were resolved by consensus.*

Results. *Twenty papers were included for SARS, but only two were comparative and were included in the primary endpoint analysis. Likewise, eleven papers were included for COVID-19, four of which were comparative and were considered for the primary outcome analysis. Included studies for both SARS and COVID-19 are mostly retrospective and highly heterogeneous, with lethality ranging from 0% to 100% and ICU admission rate ranging from 9% to 100%. Fourteen patients were included in our case series, 7 males and 7 females.*

Conclusion. *No randomised controlled trial is available yet for corticosteroids pulse-therapy defined as at least ≥500mg/day methylprednisolone in patients with emerging coronavirus pneumonia. Lethality among our cohort is high (4/14), but this finding should be interpreted with caution due to the fact that in our setting pulse-steroids were used in patients not eligible for other treatments because of comorbidities or as rescue therapy. The incidence of steroid-related adverse events seems low in our cohort.*

The quality of the evidence on glucocorticoid pulse-therapy in SARS, MERS and COVID-19 is poor. Randomised controlled trials are greatly needed.

Introduction

Pharmacologic treatments for Coronavirus Disease 2019 (COVID19) pneumonia are still under investigation. In the preliminary results of the RECOVERY trial, dexamethasone was identified as the first pharmacological therapy able to reduce mortality in COVID-19 (1). Dexamethasone 6mg for ten days improved survival in patients with respiratory failure. Off-label therapies have been widely used and there are many ongoing clinical trials, but no solid evidence of any other effective treatment is available yet.

There has been growing evidence that hyperinflammation is linked to severe pneumonia in COVID-19 (2-6). In most patients with severe disease

Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV2) infection is associated with a cytokine-storm characterised by a rise of pro-inflammatory cytokines leading to an aberrant immune response (4, 7-13). An abnormal inflammatory response is also involved in the lung damage secondary to other betacoronaviridae, as Severe Acute Respiratory Syndrome (SARS-CoV) and Middle East Respiratory Syndrome (MERS-CoV) infections (11, 14). A study by Huang *et al*. showed that people with more severe COVID-19 admitted to intensive care unit (ICU) had higher blood levels of several cytokines such as IL2, IL7, IL 10, G-CSF, IP10, MCP1, MIC1A and TNFα (4). An increment of IL6 in severe cases of betacoronaviridae infections has been described and was confirmed in SARS-CoV2 infection (12, 15-17). Neutrophils play an important role in COVID-19-induced lesions, both in the peripheral blood and lungs (3, 18). Thus, macrophage-activation syndrome-like immune activation in COVID19-associated acute respiratory distress syndrome (ARDS) has been hypothesised (19).

Consequently, researchers and clinics have been focusing on immune-modulating therapies to treat ARDS in patients with COVID-19 (3, 20, 21), including chloroquine (22), hydroxychloroquine (23), IL1-inhibitors (24), JAK-inhibitors (25) and IL-6 inhibitors (26-31).

Corticosteroids are under investigation too. They inhibit numerous pro-inflammatory cytokines, including IL-6, IL-8, MCP-1 and IL-10, that can be involved in SARS-CoV2-induced lung damage (32). Furthermore, as showed by Fauci *et al*., they block the efflux of neutrophils and monocytes to the inflammatory sites (33). Finally, research on glucocorticoids for COVID-19 can be particularly relevant for low-and-middle income countries, where expensive biologic agents may not be available on a large scale.

While low and moderate dose corticosteroids have been widely used in SARS-CoV2 infection, we sought to investigate a potential role of high dose pulse glucocorticoid therapy. In COVID-19 the cytokine storm represents the acme of the inflammatory process, suggesting the need for a prompt and strong anti-inflammatory effect, which pulse glucocorticoid therapy can provide better than non-pulse treatment. This therapy has already proven effective to treat the most severe complications of autoimmune diseases.

We designed a systematic review to further explore literature on steroid pulse therapy in SARS, MERS and COVID-19 to assess lethality, ICU admissions and the main glucocorticoids-related adverse events in these patients. The aim of this paper is to conduct a systematic literature review on safety and efficacy of pulse glucocorticoid therapy for SARS, MERS or SARS-CoV2 infection and describe a monocentric case-series of COVID-19 patients treated with off-label pulse doses of methylprednisolone.

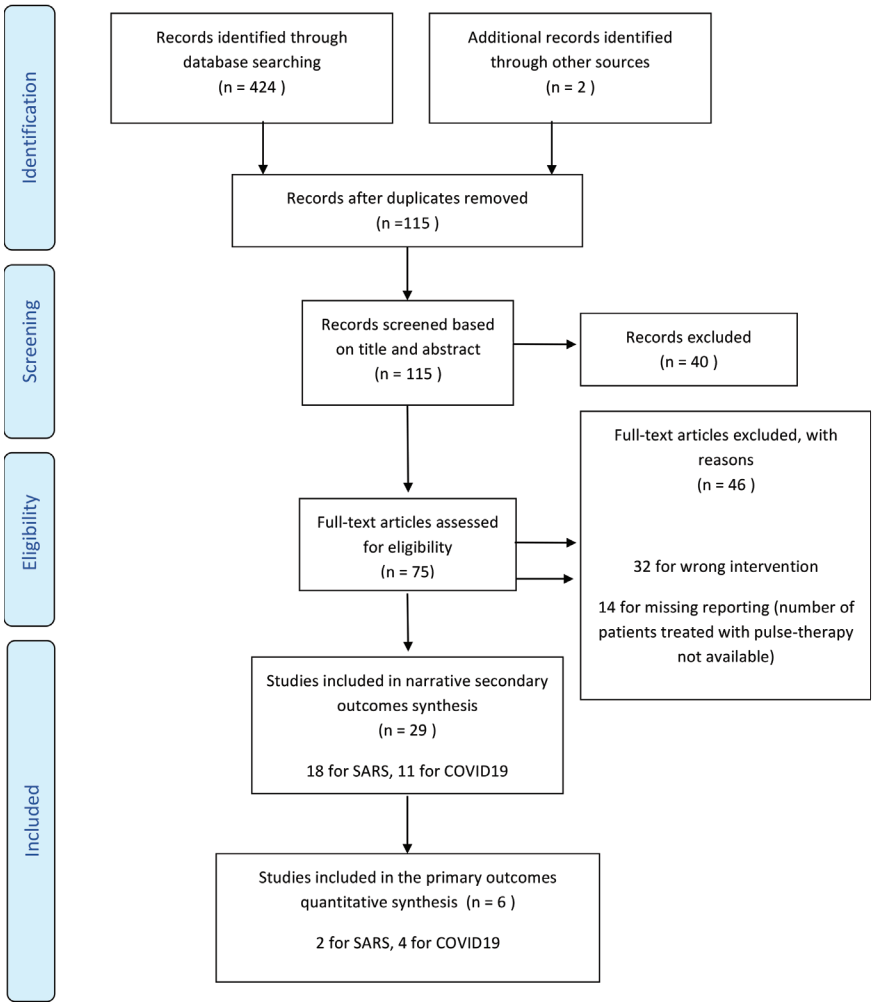

Fig. 1. PRISMA flow chart of literature search for glucocorticoids pulse-therapy in SARS-CoV, MERS-CoV and SARS CoV2.

Materials and methods

Systematic review

The review protocol was registered on PROSPERO database with ID CRD42020190183 (34). Any discrepancy with original protocol was discussed in the methods. Only papers including a methylprednisolone therapy of at least 500mg/day for at least 3 days or equivalent doses were considered. Full materials and methods of the systematic review are reported in the Supplementary file.

Patients

All consecutive patients admitted to Arcispedale Santa Maria Nuova di Reggio Emilia or Guastalla Hospital between March 1st and April 30th 2020 with COVID-19 and treated with Methylprednisolone 1 gram/day for at least three days were included in the study.

Table Ia. Primary outcomes for the two included studies for SARS.

First author	Year	Study population	Patients - pulse-therapy group	Deaths - non pulse- therapy group	Deaths - pulse-therapy group	ICU - non pulse- therapy group	ICU - pulse-therapy group
Ho[32]	2003	72 pts, 42F, 30M	17	3/55	1/17	11/55	1/17
Yam[58]	2007	1287 pts, age 29-81, 737F, 550M	220	164/1067	66/220	199/1067	48/220

Table Ib. Primary outcomes for the two included studies for COVID-19.

First author	Year	Patients - whole study	Patients - pulse-therapy group	Deaths - whole study	Deaths - pulse-therapy group	Lethality - pulse-therapy group (%)	ICU - whole study	ICU - pulse-therapy group	ICU - pulse-therapy group (%)
Fernandez-Cruz[38]	2020	463 pts, 317M, 146F, mean age 65,8 years	15	71	NA	NA	NA	NA	NA
Rodriguez-Baño[39]	2020	778pts, 552M, 226F	13	92	0	0%	NA	NA	NA
Callejas- Rubio[37]	2020	92 pts, 58M, 34F, mean age 63.9 years	26	7	NA	NA	5	NA	NA
Mareev[59]	2020	34 pts, 25M, 9F, mean age 63.5 years	17	NA	NA	NA	18	12	70.6%

Therapeutic scheme

An internal off-label therapeutic schedule was used:

Methylprednisolone intravenous 1gr single daily dose for the first 3 days;
Then methylprednisolone per os:
16mg tablet 3 times a day for 3 days;
Then methylprednisolone per os:
8mg tablet 3 times a day for 3 days;
Then methylprednisolone per os:
4mg tablet 3 times a day for 3 days;
Then methylprednisolone per os:
2mg tablet 3 times a day for 3 days.

This schedule was chosen based on rheumatologists' experience with steroid pulses in auto-immune diseases, with a 12-day tapering to avoid inflammatory rebound.

Data collection

The data were collected from both electronic and paper clinical records. Data on comorbidities, oxygen support, ventilation and infection were collected manually. A retrospective review of available computed tomography (CT) scan and chest x-ray was performed independently by two radiologists blinded to clinical data, and discordances were resolved by consensus. On the CT scan, presence of ground-glass opacities, consolidation, crazy-paving pattern, pleural effusion and lymphadenopathies (>1 cm in the short axis), as well as bilateral distribution and extension of parenchymal findings estimated by a visual scoring system (<20%, 20–39%, 40–59%, ≥60%) were collected (35). On the chest x-ray, the presence of interstitial pattern and consolidation, and the estimation of parenchymal change extension by means of the Radiographic Assessment of Lung Edema (RALE) score, were collected (36). Laboratory exams were extracted electronically.

Results

Literature review

The results found for each disease considered and the systematic review's flow-chart are depicted in Figure 1.

Eighteen papers were included for SARS, but only two were comparative and were included in the primary endpoint analysis (Table Ia). Eleven papers were included for COVID-19, four of which were comparative and were considered for the primary outcome analysis (Table Ib).

COVID-19 papers included in the primary outcome analysis

Callejas-Rubio *et al*. (37) compared a group of patients that was treated with pulse-therapy alone, another one with tocilizumab alone and the last one with tocilizumab and pulses.

Fernandez-Cruz *et al*. (38) and Callejas-Rubio *et al*. (37) had a different pulse-therapy definition compared to our inclusion criteria, as they included also doses <500mg/day of methylprednisolone. Thus, it was not possible to determine how many patients were included in the ≥500mg/day methylprednisolone group.

Rodriguez-Baño *et al*. (39) used a different definition of pulse therapy too, but data about the ≥500mg/day methylprednisolone group are provided in the Supplementary file and by contacting the corresponding author via email.

COVID-19 case series

Hussein *et al*. (40) described a single case of a woman with an anti-neutrophilic cytoplasmic antibody (ANCA) Vasculitis presenting as pulmonary haemorrage. She was treated with steroid pulses and eventually passed away.

Maideniuc *et al*. (41) described a single case of acute necrotising myelitis treated with steroid pulses, that survived and at the time of the report was undergoing rehabilitation.

Merab Sauñe *et al*. (42) described two patients treated at home with steroid pulses as rejected by medical institutions and that had favourable outcomes.

Parsons *et al*. (43) described a case of a woman developing acute disseminated encephalomyelitis (ADEM) on day 18 of hospitalisation and was treated in ICU with 5 days- 1gr methylprednisolone-pulse therapy starting on day 31. The patient was then extubated and began a rehabilitation process, being fully oriented on day 59.

Table IIa. Patients' comorbidities at baseline.

Condition	
Females/Males	7/7
Symptoms	
Cough/dyspnoea	10/14 (71.42%)
Myalgia/Asthenia	12/14 (85.71%)
Loss of consciousness	1/14 (7.14%)
Hypertension	9/14 (64.29%)
Diabetes mellitus	5/14 (35.71%)
Dementia	3/14 (21.42%)
Cerebral vascular disease	2/14 (14.29%)
COPD	2/14 (14.29%)
Obesity	2/14 (14.29%)
Smoking history	
Active smoker	1/14 (7.14%)
Ex-smoker	1/14 (7.14%)
Previous myocardial infarction	1/14 (7.14%)
Congestive heart failure	1/14 (7.14%)
Dyslipidaemia	1/14 (7.14%)
Connective tissue disease	1/14 (7.14%)
Chronic kidney disease	1/14 (7.14%)
Metastatic solid tumour	1/14 (7.14%)
HIV-infection	1/14 (7.14%)

Pugin *et al*. (44) described 5 cases of COVID19-related encephalitis treated in ICU with methylprednisolone 500 mg pulse-therapy for 5 days. After 48–72 hours, awakening with a dramatic change of the level of consciousness was observed in all patients allowing extubation in 3/5 patients (2 had been tracheostomised). Five to ten days after the first steroid pulse 3/5 patients had fully recovered and the remaining two were fluctuating with variations of arousal, but when awake their Glasgow Coma Scale (GCS) was 14.

Sheianov *et al*. (45) reported a case series of 3 patients treated first with 125mg/day of methylprednisolone, then with intravenous tocilizumab after ICU admission and intubation. Eventually, due to clinical worsening, they were treated with 1gr methylprednisolone and intravenous immunoglobins for 3 days. Notably, all of them recovered and were discharged home by day 30 after admission.

So *et al*. (46) described a series of seven intubated patients treated with 3 days-pulse therapy (500mg or 1gr of methylprednisolone) and a total duration of 13 days of corticosteroids. They were all extubated (2–7 days of mechanical ventilation) and discharged home. Piperacillin/tazobactam plus azithromycin or levofloxacin were administered for 7 days. Interestingly, in this case series no superinfection observed, while 2 cases of hyperglycaemia and delusions were reported.

The remaining results of the literature review are reported in the Supplementary file.

Case series

Fourteen patients were included in our case series, 7 males and 7 females.

The patients' characteristics at baseline are described in Table IIa. Three of them (patients no. 1, 2 and 7) were previously treated with off-label tocilizumab but did not experience any significative improvement, thus steroids pulse-therapy was used as rescue therapy with a subsequent respiratory recovery and decrease of oxygen requirement. Table IIb describes the radiological characteristics of the patients at baseline. CT scans were available in 13/14 patients, in all cases with presence of ground-glass opacities and bilateral distribution. Consolidation and crazy-paving pattern were recognised in 8/13 and 11/13 patients, respectively, while pleural effusion and lymphadenopathy were present in 4/13 patients. The visual extension of disease was <20% in 2 patients, 20–39% in 5 patients, 40–59% in 3 patients and ≥60% in 3 patients. The patient without available CT scan was judged with a high parenchymal involvement based on chest x-rays, with presence of both interstitial pattern and consolidation, and a RALE score of 17. The patients' outcomes are shown in Table III. Four out of fourteen patients died, while two returned to the nursing homes where they lived before hospital admission. Of the remaining 8 patients, 4 returned to hospital accident and emergency but only one of them needed hospital re-admission for suspected vasculitis. Episodes of delirium were witnessed for the four deceased patients and the two patients that lived in nursing homes with cognitive impairment. For the other 8 patients no episode of delirium nor psychosis was reported.

Discussion

To date, no randomised controlled trial is available for the use of corticosteroids pulse-therapy defined as ≥500mg/

Table IIb. Patients' imaging characteristics at baseline.

	CT - Ground glass opacities	CT - Consolidation	CT - Crazy Paving	CT - Bilateral	CT- Visual extension	CT- Pleural effusion	CT - Lymphadeno-pathy	x-rays - Interstitial pattern	x-rays- Consolidation	x-rays - RALE
1	Yes	No	No	Yes	<20%	No	No	No	No	0
2	Yes	No	No	Yes	20-39%	No	No	-	-	-
3	Yes	Yes	Yes	Yes	40-59%	Yes	No	Yes	No	0
4	Yes	Yes	Yes	Yes	20-39%	No	No	-	-	-
5	Yes	Yes	Yes	Yes	40-59%	No	Yes	-	-	-
6	-	-	-	-	-	-	-	Yes	Yes	17
7	Yes	Yes	Yes	Yes	≥60%	No	No	Yes	Yes	26
8	Yes	Yes	Yes	Yes	40-59%	No	No	-	-	-
9	Yes	No	Yes	Yes	<20%	Yes	No	No	Yes	6
10	Yes	No	Yes	Yes	>60%	No	No	-	-	-
11	Yes	Yes	Yes	Yes	20-39%	No	Yes	Yes	No	7
12	Yes	Yes	Yes	Yes	>60%	Yes	No	-	-	-
13	Yes	Yes	Yes	Yes	20-39%	No	NO	No	Yes	11
14	Yes	No	Yes	Yes	20-39%	No	Yes	-	-	-
Freq.	13/13	8/13	11/13	13/13		3/13	3/13	4/7	4/7	

Table IIc. Patients' laboratory characteristics at baseline.

	Pre-pulse therapy					Post-pulse therapy				
	CRP (mg/dl)	LDH (mg/dl)	D-dimer (ng/ml)	IL-6 (pg/ml)	P/F (mmHg)	CRP (mg/dl)	LDH (mg/dl)	D-dimer (ng/ml)	IL-6 (pg/ml)	P/F (mmHg)
1	4.26	628	340	25.9	216.4	0.53	628	627	nd	242.5
2	1.34	590	1097	20.23	186	0.06	509	NA	NA	334
3	6.13	1512	1632	182.8	NA	0.87	1298	1675	887.8	NA
4	15.2	359	918	112.5	195.4	1.88	380	421	NA	99.8
5	10.1	500	NA	NA	253.2	2.39	451	476	NA	136
6	1.85	922	2510	5	91.1	2.38	523	828	19.4	151.3
7	32.8	1020	1301	265.4	112.3	5.06	727	NA	NA	NA
8	11.1	530	NA	66.3	NA	1.15	472	1722	4.7	NA
9	20.1	1023	9572	192.8	108.9	10.18	4823	13246	98.1	82
10	16	879	1502	103.8	171.3	31.59	871	NA	NA	NA
11	13.7	1240	2686	89.5	NA	2.39	NA	NA	NA	NA
12	8.26	930	1617	24.1	NA	0.47	NA	1083	1.4	NA
13	4.57	662	2525	24.3	276	0.38	469	NA	NA	NA
14	13.2	829	4396	49.1	173.8	0.75	564	NA	NA	176
Median	10.6	854	1624.5	66.3	179.9	1.515	543.5	955.5	19.4	151.3

NA: not available; CRP: C-reactive protein; LDH: lactate dehydrogenasis; IL-6: interleukin-6; P/F: oxygen arterial pressure to inhaled oxygen fraction ratio.

Table III. Patients' clinical outcomes and adverse events.

	Outcome	Therapy-to-discharge or death (days)	Oxygen support duration (days)	NIV	NIV duration (days)	Infections	Re-admission	Re-admission cause
1	Home	8	13	NO	NA	Nil	NO	
2	Home	7	16	YES	3	Nil	NO	
3	Deceased	9	11	YES	10	Nil	NA	
4	Home	15	16	YES	8	Nil	NO	
5	Home	10	9	NO	NA	Nil	YES	Upper abdominal pain
6	Deceased	10	14	YES	12	Nil	NA	
7	Home	28	23	YES	10	Nil	YES	Chest pain
8	Home	21	23	NO	NA	Nil	YES	Suspect vasculitis
9	Deceased	6	6	YES	6	Suspect bacterial infection at baseline	NA	
10	Deceased	9	10	NO	NA	Nil	NA	
11	Home	10	7	NO	NA	Nil	YES	Dyspnoea and fever
12	Home	20	14	NO	NA	Nil	NO	
13	Nursing home	29	47	NO	NA	Suspect bacterial infection at baseline	NO	
14	Nursing home	26	34	NO	NA	Escherichia coli UTI	NO	
Median		10	14		9			

NIV: non-invasive ventilation; NA: not applicable; UTI: urinary tract infection.

day of methylprednisolone in patients with beta-coronaviridae-related pneumonia.

In SARS steroid pulse therapy was widely used as a rescue therapy in extremely severe patients that did not improve after other treatments. This is particularly evident in the SARS most-described cohorts in Hong Kong.

Included studies for both SARS and COVID-19 are mostly retrospective and highly heterogeneous, with lethality ranging from 0% to 100% and ICU admission rate ranging from 9% to 100%. This reasonably depends on the extremely different populations described, such as a small population of patients with end-stage renal disease (47), severely compromised patients or larger cohorts with better outcomes (39, 48, 49).

Understandably, as most of these studies were retrospective and did not particularly focus on pulse-therapy, the secondary outcomes of this systematic review were not reported for patients treated with pulse-therapy. Even for the avascular osteonecrosis and bone mineral density, the most-investigated steroid-related adverse events in SARS patients, the results are inconsistent. While there is some agreement on the duration of steroidal therapy as a major risk factor associated with avascular necrosis (50), it is unclear if high-dose but short duration therapies might be detrimental (51, 52). Furthermore, avascular osteonecrosis seems to stop or even ameliorate once glucocorticoids are ceased (53, 54).

Among the excluded papers, it is worth mentioning Edalatifard *et al*. (55) and Ruiz-Irastorza *et al*. (56). Edalatifard *et al*. (55) conducted a single-blind randomised controlled trial comparing standard of care alone with standard of care plus methylprednisolosone 250mg/day for 3 days on 68 patients with COV-

ID-19. In this study the standard of care group did not receive glucocorticoids. Methylprednisolone pulses group had a significantly higher percentage of improved patients (94.1% *vs*. 57.1%; p=0.001) and a significantly lower mortality (5.9% *vs*. 42.9%; p<0.001).

Ruiz-Irastorza *et al*. (56) conducted a comparative observational study in 242 patients with high inflammatory markers at admission. Sixty-one patients (25%) received methylprednisolone 125–250mg/day pulse-therapy for three days in the second week of disease. This pulse-therapy group had a decreased hazard ratio for death (0.35; 95%CI 0.11–1.06) and composite outcome death or intubation (0.33; 95%CI 0.13–0.84) compared to the non-pulse-therapy group.

The lethality in our case series is high (4/14) compared to the overall lethality described for COVID-19 (57). Nevertheless, this finding should be interpreted with caution due to the fact that in our setting pulse-steroids were mostly used as rescue therapy in patients with moderate to severe respiratory failure or not eligible to other treatments due to other comorbidities. The four deceased patients had important comorbidities, with a Charlson's score ranging from 4 to 7 and age ranging from 68 to 86 years. Notably, the incidence of steroid-related adverse events seems low in our cohort, but a longer follow-up is needed, particularly for avascular osteonecrosis. The previous evidence from SARS survivors suggests that avascular osteonecrosis is often asymptomatic and can improve over time (53, 54).

With regard of super-infections, only one urinary tract infection after the administration of pulse-therapy was found. New onsets of delirium were not present in our cases, as well as clinically relevant episodes of hyperglycaemia. Adverse events and in particular super-infections might be under reported in the examined literature, but this low prevalence of steroid-related adverse events is consistent with the findings of our case series.

The impact of our findings is limited by the small sample and retrospective nature of our study. However, in our small cohort, methylprednisolone pulse-therapy followed by a rapid corticosteroid reduction and suspension seemed relatively safe. While many clinicians and researchers are focusing on immune-modulatory therapies to control the cytokine storm induced by SARS-CoV2 infection, steroid pulse-therapy can be a viable option because of its fast and profound anti-inflammatory effect acting on multiple pathways. This can be particularly important considered the affordability of these treatment.

Conclusion

The quality of the evidence on glucocorticoid pulse-therapy defined as ≥500mg/day of methylprednisolone in SARS, MERS and COVID-19 is poor due to the lack of prospective studies. Randomised controlled trials are urgently needed.

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References

1. RECOVERY COLLABORATIVE GROUP *et al*.: Dexamethasone in hospitalized patients with Covid-19 – Preliminary report. *N Engl J Med* 2020 July 17 [Online ahead of print].
2. MEHTA P, MCAULEY DF, BROWN M, SANCHEZ E, TATTERSALL RS, MANSON JJ: COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; 395: 1033-4.
3. WU C, CHEN X, CAI Y *et al*.: Risk factors associated with acute respiratory distress syndrome and death in patients with Coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020; 180: 934-43.
4. HUANG C, WANG Y, LI X *et al*.: Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395: 497-506.
5. SARZI-PUTTINI P, GIORGI V, SIROTTI S *et al*.: COVID-19, cytokines and immunosuppression: what can we learn from severe acute respiratory syndrome? *Clin Exp Rheumatol* 2020; 38: 337-42.
6. FERRO F, ELEFANTE E, PUXEDDU I *et al*.: COVID-19: the new challenge for rheumatologists. First update. *Clin Exp Rheumatol* 2020; 38: 373-82.
7. HUI DSC, ZUMLA A: Severe acute respiratory syndrome: historical, epidemiologic, and clinical features. *Infect Dis Clin North Am* 2019; 33: 869-89.
8. AZHAR EI, HUI DSC, MEMISH ZA, DROSTEN C, ZUMLA A: The Middle East Respiratory Syndrome (MERS). *Infect Dis Clin North Am* 2019; 33: 891-905.
9. GUAN W-J, NI Z-Y, HU Y *et al*.: Clinical characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; 382: 1708-20.
10. LI G, FAN Y, LAI Y *et al*.: Coronavirus infections and immune responses. *J Med Virol* 2020; 92: 424-32.
11. CHANNAPPANAVAR R, PERLMAN S: Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Semin Immunopathol*. 2017; 39: 529-39.
12. MOORE JB, JUNE CH: Cytokine release syndrome in severe COVID-19. *Science*. 2020; 368: 473-4.
13. JAMILLOUX Y, HENRY T, BELOT A *et al*.: Should we stimulate or suppress immune responses in COVID-19? Cytokine and anti-cytokine interventions. *Autoimmun Rev* 2020; 19: 102567.
14. DE WIT E, VAN DOREMALEN N, FALZARANO D, MUNSTER VJ: SARS and MERS: recent insights into emerging coronaviruses. *Nat Rev Microbiol* 2016; 14: 523-34.
15. MIN C-K, CHEON S, HA N-Y *et al*.: Comparative and kinetic analysis of viral shedding and immunological responses in MERS patients representing a broad spectrum of disease severity. *Sci Rep* 2016; 6: 25359.
16. WAN S, YI Q, FAN S *et al*.: Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP). *medRxiv* February 2020 [Online ahead of print].
17. QIN C, ZHOU L, HU Z *et al*.: Dysregulation of immune response in patients with Coronavirus 2019 (COVID-19) in Wuhan, China. *Clin Infect Dis* 2020; 71: 762-8.
18. BARNES BJ, ADROVER JM, BAXTER-STOLTZFUS A *et al*.: Targeting potential drivers of COVID-19: Neutrophil extracellular traps. *J Exp Med* 2020; 217: e20200652.
19. MCGONAGLE D, SHARIF K, O'REGAN A, BRIDGEWOOD C: The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. *Autoimmun Rev* 2020; 19: 102537.
20. SANDERS JM, MONOGUE ML, JODLOWSKI TZ, CUTRELL JB: Pharmacologic treatments for Coronavirus disease 2019 (COVID-19): A review. *JAMA* 2020; 323: 1824-36.
21. ALIJOTAS-REIG J, ESTEVE-VALVERDE E, BELIZNA C *et al*.: Immunomodulatory therapy for the management of severe COVID-19. Beyond the anti-viral therapy: A comprehensive review. *Autoimmun Rev* 2020; 19: 102569.
22. COLSON P, ROLAIN J-M, LAGIER J-C, BROUQUI P, RAOULT D: Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. *Int J Antimicrob Agents* 2020; 55 :105932.
23. CHEN Z, HU J, ZHANG Z *et al*.: Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. *medRxiv* January 2020 [Online ahead of print].
24. AOUBA A, BALDOLLI A, GEFFRAY L *et al*.: Targeting the inflammatory cascade with anakinra in moderate to severe COVID-19 pneumonia: case series. *Ann Rheum Dis*. 2020; 79: 1381-2.

25. SPINELLI FR, CONTI F, GADINA M: HiJAKing SARS-CoV-2? The potential role of JAK inhibitors in the management of COVID-19. *Sci Immunol* 2020; 5: eabc5367.
26. TONIATI P, PIVA S, CATTALINI M *et al*.: Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: a single center study of 100 patients in Brescia, Italy. *Autoimmun Rev* 2020; 19: 102568.
27. ZHANG C, WU Z, LI J-W, ZHAO H, WANG G-Q: The cytokine release syndrome (CRS) of severe COVID-19 and interleukin-6 receptor (IL-6R) antagonist tocilizumab may be the key to reduce the mortality. *Int J Antimicrob Agents* 2020; 55: 105954.
28. STONE JH, TUCKWELL K, DIMONACO S *et al*.: Trial of tocilizumab in giant-cell arteritis. *N Engl J Med* 2017; 377: 317-28.
29. HERMINE O, MARIETTE X, THARAUX P-L *et al*.: Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: a randomized clinical trial. *JAMA Intern Med* 2021; 181: 32-40.
30. SALVARANI C, DOLCI G, MASSARI M *et al*.: Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized clinical trial. *JAMA Intern Med* 2021; 181: 24-31.
31. GUARALDI G, MESCHIARI M, COZZI-LEPRI A *et al*.: Tocilizumab in patients with severe COVID-19: a retrospective cohort study. *Lancet Rheumatol* 2020; 2: e474-84.
32. HO JC, OOI GC, MOK TY *et al*.: High-dose pulse versus nonpulse corticosteroid regimens in severe acute respiratory syndrome. *Am J Respir Crit Care Med* 2003; 168: 1449-56.
33. FAUCI AS, DALE DC, BALOW JE: Glucocorticosteroid therapy: mechanisms of action and clinical considerations. *Ann Intern Med* 1976; 84: 304-15.
34. DOLCI G, CASSONE G, COSTANTINI, BESUTTI G, MASSARI M, SALVARANI C: Glucocorticoids pulse-therapy for SARS-CoV, MERS-CoV and SARS-CoV-2 pneumonia: a systematic review and meta-analysis. PROSPERO. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020190183. Published 2020.
35. COLOMBI D, BODINI FC, PETRINI M *et al*.: Well-aerated lung on admitting chest CT to predict adverse outcome in COVID-19 pneumonia. *Radiology* 2020; 296: E86-96.
36. WONG HYF, LAM HYS, FONG AH-T *et al*.: Frequency and distribution of chest radiographic findings in COVID-19 positive patients. *Radiology* 2020; 296: E72-78.
37. CALLEJAS RUBIO JL, LUNA DEL CASTILLO J DE D, DE LA HERA FERNÁNDEZ J, GUIRAO ARRABAL E, COLMENERO RUIZ M, ORTEGO CENTENO N: Effectiveness of corticoid pulses in patients with cytokine storm syndrome induced by SARS-CoV-2 infection. *Med Clin* (Engl Ed) 2020; 155: 159-61.
38. FERNÁNDEZ-CRUZ A, RUIZ-ANTORÁN B, MUÑOZ-GÓMEZ A *et al*.: A retrospective controlled cohort study of the impact of glucocorticoid treatment in SARS-CoV-2 infection mortality. *Antimicrob Agents Chemother* 2020; 64: e01168-20.
39. RODRÍGUEZ-BAÑO J, PACHÓN J, CARRATALÀ J *et al*.: Treatment with tocilizumab or corticosteroids for COVID-19 patients with hyperinflammatory state: a multicentre cohort study (SAM-COVID-19). *Clin Microbiol Infect* 2020 Aug 27 [Online ahead of print].
40. HUSSEIN A, KHALIL KAL, BAWAZIR YM: Anti-neutrophilic cytoplasmic antibody (ANCA) vasculitis presented as pulmonary hemorrhage in a positive COVID-19 patient: a case report. *Cureus* 2020; 12: e9643
41. MAIDENIUC C, MEMON AB: Acute necrotizing myelitis and acute motor axonal neuropathy in a COVID-19 patient. *J Neurol* 2020 Aug 9 [Online ahead of print].
42. SAUÑE PM, BRYCE-ALBERTI M, PORTMANN-BARACCO AS, ACCINELLI RA: Methylprednisolone pulse therapy: An alternative management of severe COVID-19. *Respir Med Case Rep* 2020; 31: 101221.
43. PARSONS T, BANKS S, BAE C, GELBER J, ALAHMADI H, TICHAUER M: COVID-19-associated acute disseminated encephalomyelitis (ADEM). *J Neurol* 2020; 267: 2799-802.
44. PUGIN D, VARGAS M, THIEFFRY C, SCHIBLER M: COVID-19-related encephalopathy responsive to high-dose glucocorticoids. *Neurology* 2020; 95: 543-6.
45. SHEIANOV M V, UDALOV YD, OCHKIN SS, BASHKOV AN, ALEKSANDR S: Pulse therapy with corticosteroids and intravenous immunoglobulin in the management of severe tocilizumab-resistant COVID-19: A report of three clinical cases. *Cureus* 2020; 12: e9038
46. SO C, RO S, MURAKAMI M, IMAI R, JINTA T: High-dose, short-term corticosteroids for ARDS caused by COVID-19: a case series. *Respirol Case Rep* 2020; 8: e00596.
47. WONG P-N, MAK S-K, LO K-Y *et al*.: Clinical presentation and outcome of severe acute respiratory syndrome in dialysis patients. *Am J Kidney Dis* 2003; 42: 1075-81.
48. SUNG JJY, WU A, JOYNT GM *et al*.: Severe acute respiratory syndrome: report of treatment and outcome after a major outbreak. *Thorax* 2004; 59: 414-20.
49. TSUI PT, KWOK ML, YUEN H, LAI ST: Severe acute respiratory syndrome: clinical outcome and prognostic correlates. *Emerg Infect Dis J* 2003; 9: 1064.
50. CHAN MHM, CHAN PKS, GRIFFITH JF *et al*.: Steroid-induced osteonecrosis in severe acute respiratory syndrome: a retrospective analysis of biochemical markers of bone metabolism and corticosteroid therapy. *Pathology* 2006; 38: 229-35.
51. GRIFFITH JF, ANTONIO GE, KUMTA SM *et al*.: Osteonecrosis of hip and knee in patients with severe acute respiratory syndrome treated with steroids. *Radiology* 2005; 235: 168-75.
52. LAU EMC, CHAN FWK, HUI DSC, WU AKL, LEUNG PC: Reduced bone mineral density in male Severe Acute Respiratory Syndrome (SARS) patients in Hong Kong. *Bone* 2005; 37: 420-4.
53. ZHANG P, LI J, LIU H *et al*.: Long-term bone and lung consequences associated with hospital-acquired severe acute respiratory syndrome: a 15-year follow-up from a prospective cohort study. *Bone Res* 2020; 8: 8.
54. GRIFFITH JF: Musculoskeletal complications of severe acute respiratory syndrome. *Semin Musculoskelet Radiol* 2011; 15: 554-60.
55. EDALATIFARD M, AKHTARI M, SALEHI M *et al*.: Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial. *Eur Respir J* 2020; 56: 2002808.
56. RUIZ-IRASTORZA G, PIJOAN J-I, BERECIARTUA E *et al*.: Second week methyl-prednisolone pulses improve prognosis in patients with severe coronavirus disease 2019 pneumonia: An observational comparative study using routine care data. *PLoS One* 2020; 15: e0239401.
57. WHO Coronavirus Disease (COVID-19) Dashboard. https://covid19.who.int/. Accessed May 31, 2020.
58. YAM LY-C, LAU AC-W, LAI FY-L, SHUNG E, CHAN J, WONG V: Corticosteroid treatment of severe acute respiratory syndrome in Hong Kong. *J Infect* 2007; 54: 28-39.
59. MAREEV VY, ORLOVA YA, PAVLIKOVA EP *et al*.: [Steroid pulse-therapy in patients with Coronavirus pneumonia (COVID-19), systemic inflammation and risk of venous thrombosis and thromboembolism (WAYFARER Study)]. *Kardiologiia* 2020; 60: 15-29.