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REVIEW

Beware of Steroid-Induced Avascular Necrosis of the Femoral Head in the Treatment of COVID-19—Experience and Lessons from the SARS Epidemic

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Summary: The recent outbreak of coronavirus disease 2019 (COVID-19) has become a global epidemic. Corticosteroids have been widely used in the treatment of severe acute respiratory syndrome (SARS), and the pathological findings seen in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are very similar to those observed in severe acute respiratory syndrome-related coronavirus (SARS-CoV) infection. However, the long-term use of corticosteroids (especially at high doses) is associated with potentially serious adverse events, particularly steroid-induced avascular necrosis of the femoral head (SANFH). In today's global outbreak, whether corticosteroid therapy should be used, the dosage and duration of treatment, and ways for the prevention, early detection, and timely intervention of SANFH are some important issues that need to be addressed. This review aims to provide a reference for health care providers in COVID-19 endemic countries and regions.

Article Focus: Hormones are a double-edged sword. This review aims to provide a reference for health care providers in coronavirus disease 2019 (COVID-19) endemic countries and regions, especially with respect to the pros and cons of corticosteroid use in the treatment of patients with COVID-19.

Key Messages: In today's global outbreak, whether corticosteroid therapy should be used, the dosage and duration of treatment, and ways for the prevention, early detection, and timely intervention of SANFH are some important issues that need to be addressed.

Strengths and Limitations: Since SARS was mainly prevalent in China at that time, many evidences in this paper came from the reports of Chinese scholars. There is a bias in the selection of data, which may ignore the differences in environment, race, living habits, medical level and so on. SANFH may be the result of multiple factors. Whether the virus itself is an independent risk factor for SANFH has not been confirmed. In this paper, through literature retrieval, some reference opinions on glucocorticoid usage, diagnosis and treatment of SANFH are given. However, due to the lack of large-scale research data support, it can not be used as the gold standard for the above problems.

Keywords: COVID-19, steroid, necrosis of the femoral head, SARS

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Search Strategy and Selection Criteria

We searched the ScienceDirect, PubMed, MEDLINE, and Wiley (between January 2003, and August 2020) for articles published from the inception of each database. We used the search terms "SARS" or "COVID-19" in combination with

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the terms ("ARDS" or "respiratory system") and ("steroid" or "glucocorticoid" or "steroid-induced") with ("necrosis of the femoral head" or "necrosis"). We largely selected articles published in the past 15 years, but we did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant.

Introduction

The recent outbreak of the coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a pandemic. It was found that the amino acid sequence of the spike (S) protein of SARS-CoV-2 was 76·47% similar to that of severe acute respiratory syndrome-related coronavirus (SARS-CoV), but its affinity for angiotensin-converting enzyme 2 (ACE2) was 10 to 20 times higher than that of the latter, resulting in rapid transmission between people.[1] Huang et al reported that fever (98%) and cough (76%) were the initial features of the disease. 55% of the patients developed dyspnea after an average of 8 days of illness onset, and 29% of the patients developed ARDS 9 days after illness onset.[2] The pathological results showed that ARDS played an important role in the death of COVID-19 patients. Further, autopsy revealed bilateral diffuse alveolar injury with exudation of fibrous mucus and a mononuclear inflammatory infiltrate dominated by lymphocytes in the lung interstitium, which were related to the cytokine storm induced by overactivation of the immune system. These findings were very similar to those observed in SARS-CoV infection.[3] Corticosteroids have been widely used in the treatment of severe acute respiratory syndrome (SARS). During the SARS epidemic of 2003, corticosteroids were considered to improve the patient's condition in the early stages by reducing fever, reducing lung inflammatory infiltration, and improving oxygenation; however, long-term use (especially at high doses) is associated with potentially serious adverse events.[4] In a follow-up study, 23.1% (18 of 78) of Chinese patients with SARS developed steroid-induced avascular necrosis of the femoral head (SANFH) which was mainly due to the administration of high-dose glucocorticoids during the treatment of SARS.[5] However, most of the studies ignored the influence of other confounding factors when analyzed the relationship between steroid and osteonecrosis of the femoral head(ONFH) retrospectively. There are many factors to be looked for, such as hemoglobinopathies (especially sickle cell anemia), autoimmune diseases, hyperlipidemia, excessive alcohol intake and abuse of traditional Chinese medicine.[6] For example, the steroid dose is positively correlated with the incidence of osteonecrosis in systemic lupus erythematosus patients. The rate of osteonecrosis increased when prednisone-equivalent > 20 mg/d, each 10 mg/d increase was associated with a 3.6% increase.[7] In addition, prior osteoporotic status and vitamin D deficiency of patients can not be ignored. Gangji confirmed that ONFH is associated with low bone mineral density.[8] Inoue reported that the serum concentration of 1.25 (OH) 2D3 in 18 patients with idiopathic ONFH (16.7 ± 7.9 pg/mL) was significantly lower than that in the control group (26.9 ± 13.7 pg/mL) ($P < 0.01$), suggesting the possibility of bone metabolism abnormalities due to abnormal vitamin D3 metabolism as a background of ONFH.[9] It has also been suggested that SARS itself may be an independent risk factor for ONFH.[10]

The prognosis of untreated SANFH is poor; it often leads to subchondral collapse in a short time. Timely diagnosis and treatment can preserve the function of the hip joint to the maximum extent only if detected in the early stages. Hormones are a double-edged sword. In today's global outbreak, whether corticosteroid therapy should be used, the dosage and duration of treatment, and ways for the prevention, early detection, and timely intervention of SANFH are some important issues that need to be addressed. We hope that this review can provide a reference for health care providers in COVID-19 endemic countries and regions, especially with respect to the pros and cons of corticosteroid use in the treatment of patients with COVID-19.

Mechanism of Action of Glucocorticoids

The inflammation and cytokine storm caused by the immune response are responsible for the fatal pneumonia after SARS-CoV infection.[11] Cytokines such as interferon gamma (IFN-γ), tumour necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6) can cause tissue damage.[12] It is well known that corticosteroids do not directly inhibit viral replication, but their main effects are anti-inflammatory and immunosuppressive. Glucocorticoids can inhibit the "cytokine storm" by inhibiting the expression of proinflammatory proteins such as IL-1, IL-2, IL-6, TNF-α, and IFN-γ and the migration of leukocytes to the sites of inflammation.[13]

Glucocorticoids can also affect lipid metabolism. If the emulsification of very low-density lipoprotein cholesterol in the blood is not complete, it will combine with the lipoprotein globules which can form fat emboli resulting in blockage of the peripheral blood vessels and, consequently, ischaemic necrosis of the bone tissue in the vascular supply area. At the same time, the free fatty acids produced by hydrolysis of the fat emboli damage the capillary endothelial cells, cause diffuse vasculitis, and trigger intravascular coagulation, all of which aggravate the ischaemic necrosis of bone tissue.[14] Glucocorticoids can also regulate the local blood flow by regulating the response of the blood vessels to vasoactive substances, which leads to constriction of the internal artery of the femoral head resulting in femoral head ischaemia.[15] Fu et al found that the expression of microRNA 596 (*miR-596)* in the bone marrow of patients with steroid-induced femoral head necrosis (FHN) was upregulated, which could hinder the repair of the osteonecrotic bone by inhibiting the proliferation and osteogenic differentiation of the bone marrow stromal cells (BMSCs).[16] Some basic studies have found that microRNA-17-5p (*miR-17-5p*) and *miR-210* are related to the pathogenesis of SANFH.[17,18] Du et al confirmed for the first time that four sensitive single-nucleotide polymorphisms (SNPs), namely, rs3740938, rs2012390, rs1940475, and rs11225395 of *MMP8* from the MMP (matrix metalloproteinases)/TIMP (tissue inhibitors of MMP) system were significantly correlated with the increased risk of steroid-induced FHN in a study conducted in northern China.[19] Wang et al considered that −1*031CT/CC* and −8*63 AC* genotypes may be risk factors for FHN in patients with SARS.[20]

Pros and Cons of Glucocorticoid Therapy

There is no specific drug for the treatment of COVID-19. Fever, cough, and dyspnoea are the most common symptoms of COVID-19. Symptomatic supportive treatment is still the most effective treatment. ARDS is a serious complication of COVID-19 and the use of glucocorticoids in the treatment of severe COVID-19 pneumonia and ARDS is controversial. Herein, we compiled a table including opinions (Table 1) and research details in the treatment of COVID-19 pneumonia and ARDS, and present the points in favour of and against the use of glucocorticoids.

Favor

It is well known that corticosteroids are beneficial in the treatment of ARDS because they reduce inflammation and improve the functioning of the lung and extrapulmonary organs. Experiments on animals have also shown that inhibition of inflammation can improve the prognosis of animals infected with SARS-CoV.[36] Russell et al summarised the clinical evidence indicating that corticosteroids can be used in patients with SARS-CoV infection.[37] A large number of retrospective studies have also shown that the corticosteroids prescribed to the vast majority of SARS patients may contribute to the regulation of the inflammatory response and treatment of lung injury.[38] Chen et al, through a retrospective study of 401 patients with severe SARS, found that the appropriate application of glucocorticoids in patients with severe SARS can significantly reduce mortality and shorten the length of hospital stay.[39] A total of 2141 patients with influenza A (H1N1) viral pneumonia from 407 hospitals in China received five kinds of low-dose corticosteroids (25–150 mg/day methylprednisolone or equivalent) which significantly reduced the mortality in patients with PaO_2/FiO_2 < 300 mmHg.[40] The genome structure, transmission, and pathogenesis of SARS-CoV-2 are similar to those of SARS-CoV. In view of the fact that there is no conclusive evidence at present and there is an urgent need in clinical practice, the National Health Commission of China suggests that methylprednisolone should be used appropriately within a short period of time (3–5 days) onset of pneumonia and at a dose not exceeding 1–2 mg/kg/day. This method may achieve a good therapeutic effect in patients with a strong inflammatory response and acute progression of the disease observed by lung imaging.[41] Extensive inflammation, which is caused by excessive activation of proinflammatory cytokines and chemotaxis of T lymphocytes to the inflammatory site, is the possible mechanism of the chest tightness and dyspnoea in COVID-19. Short-term and low-dose corticosteroid treatment can quickly relieve the symptoms of chest tightness and dyspnoea.[42] Some scholars believe that this treatment should not be limited to severely ill patients because the early use of corticosteroids can reduce the risk of ARDS in viral infections.[43] The utilisation rate of glucocorticoids in COVID-19 patients reported by many hospitals in China was 28.0% to 44.9%,[44–46] and even 70% in some critically ill patients.[47] This was due to their experience of treating patients with similar medications during the SARS-Co-V epidemic. A retrospective cohort study of 201 patients with confirmed COVID-19 pneumonia at the Wuhan Jinyintan Hospital showed that methylprednisolone treatment may be beneficial to patients with ARDS.[48] Recent

Table 1 Main Characteristics and Findings of the Studies About COVID-19 Patients Using Steroids

Author/ Country	Study Design	Sample Size	Grouping	Age	Male Gender	Patient Condition	Mortality	Interventions/ Treatments	Recommendation
[21]Galvez-Romero JL/ Mexico	Open-label, non-randomized study	209	Steroids/CsA plus steroids	54.06 ±13.8/55.3 ±13.3	61%/69%	Moderate or severe	35%/22% (p=0.02)	Methylprednisolone (0.5 mg/kg IV QD) or Prednisone(25 mg PO QD) up to 10 days; CsA (1–2 mg/kg PO QD) for 7 days	CsA plus steroids can reduce mortality of patients with moderate to severe disease
[22]Reiichiro Obata/ America	Retrospective study	226	Steroids/No steroids	70 (59.5,79)/ 64(51, 76)	50.9%/ 59.2%	COVID-19 patients	OR[95% CI]:1.02, [0.60–1.73],(p=0.94)	Not mentioned	Steroids did not decrease or increase in-hospital mortality
[23]Ana Fernández-Cruz/Spain	Retrospective controlled cohort study	463	Steroids/No steroids	65.4/68.1	69.7%/ 61.2%	Moderate or severe ARDS	26.2%/60% (P=0.014)	1 mg/kg/day methylprednisolone for 10 days (IQR, 8 −13); 250 −500 mg/day methylprednisolone for 3 pulses (IQR, 2–4).	Glucocorticoids(initial regimen or pulses) can reduce mortality of patients with COVID-19
[24]Kota Murohashi/ Japan	Cases report	11	Favipiravir plus methylprednisolone	63.2	73%	Severe	None	Favipiravir (1.8 g BID on day 1, followed by 0.8 g BID for a total of 14 days) plus Methylprednisolone (80, 250, or 500 mg/day) for 3–6 days.	The early-stage use of a combination of favipiravir and methylprednisolone in severe cases can achieve a favorable clinical outcome
[25]Alejandro Rodríguez-Molinero/ Spain	Cohort study	418	Steroids/No steroids	65.4	56.9%	COVID- 19 patients with pulmonary involvement	6 (8.1%)/10(13.2%)	Methylprednisolone 1 mg/kg/day or dexamethasone 20–40 mg/day	The mortality can not been analysed due to the low number of events. There is no benefit in the use of glucocorticoids in terms of lung function or time to discharge

[26]Yan Hu/ China	Single-center study	308	Steroids/No steroids	54 (44–63)/ 48 (39–60)	47.2%/ 46.7%	COVID- 19 patients with pulmonary involvement	None	Equivalent of methylprednisolone 0.75–1.5 mg/kg/d)	Glucocorticoid therapy did not significantly influence the clinical course, adverse events nor the outcome of COVID-19 pneumonia
[27]Muhammad A. Rana/PAK	Retrospective quasi-experimental study	60	Dexamethasone/ Methylprednisolone	53.8/53.9	66.7%/ 70%	Patients treated in HDU/ICU and had been on bi-level positive airway pressure.	Not mentioned	Dexamethasone 8 mg BID/Methylprednisolone 40 mg BID; 8 days	Dexamethasone is more effective in improving the P/F ratio in COVID-19 patients compared to methylprednisolone
[28]Marla J Keller/UAS	Observational study	1806	Steroids/No steroids	61.7 ± 15.9/62.3 ± 17.9	49.3%/ 46.3%	COVID-19 patients	Glucocorticoid increased mortality of patients with CRP< 10 mg/dL	Early glucocorticoids (within 48 hours of admission)	Choosing the right patients is critical to maximize the likelihood of benefit and minimize the risk of harm
[29]Hong-Ming Zhu/China	Single-center retrospective study	102	Steroids/No steroids	Not mentioned	49.3%/ 57.6%	Severe or critically ill	log-rank 0.199, P = 0.655	Methylprednisolone 0.75–1.5 mg/kg/d, < 14 days	Methylprednisolone treatment does not improve prognosis in severe and critical COVID-19 patients
[30]Malgorzata Mikulska/Italy	Observational single-center study	196	SOC plus early inflammatory treatment/SOC	64.5/73.5	70%/62%	COVID-19 patients who were not intubated	HR_{OW} = 0.48 95% CI, 0.23–0.99; p = 0.049	Tocilizumab (8mg/kg IV or 162mg subcutaneously) or methylprednisolone 1 mg/kg or both; 5 days	Early administration of tocilizumab, methylprednisolone or both can mitigate he negative impact of immune response in COVID-19
[31]V. Spagnuolo/ Italy	Retrospective study	280	Steroids/No steroids	67 (54–77)/ 62 (53–73)	78%/ 77.4%	Moderate & severe	6.8%/3.6%, (p = 0.29)	Initial methylprednisolone 0.87 (0.51–1.0) mg/Kg, discontinuation 0.38 (0.21–0.53) mg/Kg; 9 (7–16) days	SARS-CoV-2 clearance was not associated with corticosteroid use but older age or a more severe disease

(*Continued*)

Table 1 (Continued).

Author/ Country	Study Design	Sample Size	Grouping	Age	Male Gender	Patient Condition	Mortality	Interventions/ Treatments	Recommendation
[32]WHO REACT Working Group	Prospective meta-analysis	1703	Steroids/No steroids	60(52–68)	71%	Critically ill	Summary OR, 0.66 [95% CI, 0.53–0.82]; P < 0.001 based on a fixed-effect meta-analysis	Dexamethasone 15 mg/d, hydrocortisone 400 mg/d, or methylprednisolone 1 mg/kg/d	Compared with usual care or placebo, systemic corticosteroids was associated with lower 28-day all-cause mortality
[33]Soumya Sarkar/India	Meta-analysis	15,754	Steroids/No steroids	Not mentioned	Not mentioned	COVID-19 patients	OR = 1.94, 95% CI: 1.11–3.4, I^2 = 96%	Methylprednisolone equivalent ≤ 40 mg/day or ≥ 50 mg/day	Steroid increased mortality
[34]Xiaofan Lu/ China	Retrospective study	244	Steroids/No steroids	62 (50–71)	52%	Critically ill	Every 10-mg increase in dosage was associated with additional 4% mortality risk (adjusted HR 1.04, 95% CI 1.01–1.07)	Hydrocortisonee 200 mg/day (range 100–800), 8 days(4–12).	Corticosteroid must be commenced with caution
[35]Peter Horby/UK	Controlled, open-label trial	6425	Steroids/No steroids	66.9±15.4/ 65.8±15.8	64%/64%	COVID-19 patient	22.9%/25.7% (age-adjusted rate ratio, 0.83; 95% confidence interval [CI], 0.75 to 0.93; P<0.001)	Dexamethasone 6 mg QD, PO or IV,10 days	Dexamethasone can reduce mortality of patients who were receiving either invasive mechanical ventilation or oxygen alone but not among those receiving no respiratory support

Abbreviations: CsA, cyclosporine-A; IV, intravenous; QD, quaque die; PO, per os; COVID-19, coronavirus disease-2019; OR, odds ratio; CI, confidence interval; ARDS, acute respiratory distress syndrome; IQR, interquartile range; BID, bis in die; HDU, high-dependency unit; ICU, intensive care unit; P/F, partial oxygen pressure (PaO2)/inspired oxygen fraction (FiO2); CRP, C-reactive protein; SOC, standard of care; HR, hazard ratio; OW, overlap weights; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; REACT, Rapid Evidence Appraisal for COVID-19 Therapies.

multicentre studies have shown that Early administration of dexamethasone could reduce duration of mechanical ventilation and overall mortality in patients with established moderate-to-severe ARDS.[49] Although the World Health Organisation (WHO) does not recommend the routine use of glucocorticoids in patients with COVID-19, some scholars believe that the uncertain clinical evidence should not be the reason for abandoning corticosteroids in the treatment of COVID-19. At the very least, corticosteroids can be prescribed to the right patients at the right time. For example, in the context of cytokine storms, if tocilizumab is ineffective, steroid immunosuppression can be considered.[50] The results of a systematic review and meta-analysis by Yang et al revealed that patients with a severe illness were more likely to need corticosteroid treatment.[51] Therefore, it is suggested that in the treatment of patients with COVID-19, corticosteroids should not be administered to patients with a mild illness but can be used in moderate doses in patients with a severe illness to inhibit the immune response and relieve symptoms.

Opposition

During the SARS outbreak, systemic corticosteroids were widely used. However, a systematic review of the published literature on their application in SARS concluded that the treatment was not beneficial. In Stockman's meta-analysis on the use of steroids in SARS, the idea of using corticosteroids to treat ARDS was conjectured, for 25 studies were inconclusive and only four were conclusive, all of which showed that corticosteroid use was harmful.[52] Moreover, corticosteroids may damage the innate antiviral immune response. If given before virus replication is controlled, they may delay virus clearance leading to aggravation of the disease and complications of corticosteroid treatment in survivors.[53,54] In Wuhu, corticosteroid therapy is widely used in patients with COVID-19, but there is no evidence of any clinical benefits from its use in patients who do not have ARDS.[55] In the preliminary data of a COVID-19 retrospective cohort study in China, corticosteroids were used more frequently in patients who died (48%) than in patients who survived (23%).[56] Some people think that most of the patients in the above studies are critically ill patients with ARDS, and the ability of steroids to improve the (poor) prognosis in such cases is overestimated.[57] Moreover, health care providers tend to use corticosteroids for the most critical patients. Therefore, the presence of a selection bias and confounding factors may result in a biased conclusion. In the absence of solid scientific evidence, the WHO and Centers for Disease Control and Prevention (CDC) recommend that corticosteroids should not be routinely used in the treatment of viral pneumonia or ARDS in patients with COVID-19 unless otherwise indicated, such as during asthma, exacerbation of chronic obstructive pulmonary disease, or septic shock.[37] Zha et al reported that 11 out of 31 patients with COVID-19 received corticosteroid treatment (40 mg methylprednisolone was administered once or twice a day within 24 hours of admission for an average of 5 days). Cox proportional hazard regression analysis showed that there was no correlation between corticosteroid treatment and the virus clearance time, hospital stay, or symptom duration.[55] In cases where the advantage is uncertain, the complications are definite. In one study, 39% patients with SARS developed FHN within a few months of glucocorticoid treatment.[58] Furthermore, in another study, some patients who received corticosteroids for less than 4 weeks or received fewer corticosteroids, too, developed FHN.[59] But some scholars believe that SARS virus itself is an independent factor for the occurrence of femoral head necrosis.[10] Ksiazek shown that SARS virus may directly cause ONFH through S protein.[60] In addition, we believe that the strong systemic inflammatory response to release a large number of inflammatory mediators, patients with varying degrees of hypoxemia in the course of the disease can also lead to ONFH. COVID-19 patients may also suffer these pathological processes. So, we think it is irrational to deny the positive therapeutic effect of glucocorticoids. At least for those critically ill patients, saving their lives is the most important thing.

In addition, when evaluating the effect of steroid therapy, we should not ignore the role of other confounding factors. Vitamin D3, for example, may have some extra-skeletal effects, especially on the immune system and lung function.[61] The main complication of COVID-19 is ARDS mediated by a variety of mechanisms that may be aggravated by vitamin D deficiency and tapered down by activation of the vitamin D receptor.[62] Anweiler found bolus vitamin D3 supplementation during or just before COVID-19 was associated in frail elderly with less severe COVID-19 and better survival rate, indicating Vitamin D3 supplementation may be effective for COVID-19 treatment.[63]

Of course, in addition to causing SANFH, other complications caused by hormones can not be ignored. Osteoporosis, adrenal suppression, hyperglycemia, dyslipidemia, cardiovascular disease, Cushing's syndrome,

mental disorders and immunosuppression are also serious side effects in the treatment of systemic corticosteroid.[64] Although high-dose glucocorticoid pulse therapy has a rapid anti-inflammatory effect, it also increases the neutrophil/lymphocyte ratio and D-dimer level, increasing the risk of thromboembolism.[65] For newly diagnosed diabetic patients, frequent use of glucocorticoids may exacerbate hyperglycemia.[66] Obata et al found that the bacterial infection rate (25%/13.1%, P = 0.041) and fungal infection rate (12.7%/0.7%, P < 0.001) during hospitalization in steroid group were significantly higher than those in non steroid treatment group.[22] There have also been reports about glucocorticoid caused bacterial endocarditis, strongyloides or amebic infections that can progress to catastrophic complications in patients with COVID-19 pneumonia.[67,68]

Glucocorticoid Usage

The sequelae of SARS are closely related to the dosage of the hormone, duration of hormone use, sensitivity of patients to the hormone, and method of administration.[69]

Maximum Daily Dose

In one study, logistic regression analysis showed that there was a correlation between the maximum daily dose of glucocorticoids and FHN, suggesting that adequate control of the maximum daily dose is necessary.[70] Motomura et al treated rabbits with 1 mg/kg, 5 mg/kg, 20 mg/kg, and 40 mg/kg methylprednisolone; the incidence of osteonecrosis was 0%, 42%, 70%, and 96%, respectively.[71] By comparison (5 mg/kg/day vs 1 mg/kg/day), Marsh et al found that osteonecrosis only occurred in the 5 mg/kg/day group.[72] Massardo et al reported that a dose of prednisone greater than 40 mg/day was positively correlated with osteonecrosis,[73] and the incidence rate increased by 3.6% for every 10 mg increase in the dose.[7]

Cumulative Dose

In a retrospective study of 539 SARS patients treated with corticosteroids, the increased incidence of FHN was associated with the total dose of corticosteroids.[74] Griffith et al reported that the risk of FHN was 0.6% in patients receiving less than 3 g of prednisolone equivalent dose and 13% for doses greater than 3 g.[75] Zhao et al observed a nonlinear relationship between the cumulative dose and osteonecrosis. When the total dose of methylprednisolone was less than 5 g, the risk of osteonecrosis was still relatively low. However, as the total dose increased from 5 g to 10 g, the risk of osteonecrosis increased. The risk seemed to be the highest when the total dose was about 10 g to 15 g. It is considered that a low cumulative dose of corticosteroids (methylprednisolone < 5 g) is relatively safe for patients with SARS. Doctors should avoid using high-dose corticosteroids, especially those with cumulative doses > 10 g.[76] A study by Rademaker et al suggested that 700 mg prednisolone was the threshold for the occurrence of femoral head necrosis.[77] Michael et al suggested that cumulative doses > 2000 mg of methylprednisolone, > 1900 mg of hydrocortisone, > 1340 mg of hydrocortisone equivalent, and > 13,340 mg of corticosteroid therapy were risk predictors of osteonecrosis.[78]

Duration of Medication

Zhao et al reported that the incidence of osteonecrosis was closely related to the duration of treatment in 1137 patients with SARS. The rate ratio (RR) of osteonecrosis was 1.29 (95% CI 1.09–1.53, P = 0.003) for every 10 days of treatment. The relationship was nonlinear. They also asserted that it was important to reduce the risk of osteonecrosis by modifying the duration of corticosteroid treatment.[76]

Individual Differences

Li et al conducted a comprehensive investigation on the bone and joint complications of patients with SARS and found that approximately 30% of patients had osteonecrosis, but the remaining patients (about 70%), who were infected with the same type of pathogens, did not show any complications with the same corticosteroid regimen,[79] indicating that there were differences in patients' susceptibility levels. Shigemura et al found that age was a risk factor, and the risk of osteonecrosis in adolescents and adults was significantly higher than that in children.[80] Zhao et al found that there was no significant difference in the risk based on sex (RR 0.01, 95% CI 0.03–0.06, P = 0.582).[76] Kerachian et al suggested that the difference in the incidence rate may depend on the duration of medication, dosage, or some potential diseases.[15]

Timing of Medication

The timing of glucocorticoid administration is very important for the prognosis of critically ill patients. Premature administration of glucocorticoids can inhibit the initiation of immune defence mechanisms, thus increasing the viral load and eventually leading to adverse consequences. Timely administration of glucocorticoids in the early stage of the inflammatory cytokine storm can effectively

prevent the occurrence of ARDS.[81] The clinical features of this period are the rapid progress of inflammatory infiltration and a deterioration in the level of oxygenation. In other words, if there is a significant progression of the lung lesions within 48 hours in mildly ill patients, glucocorticoid treatment can be considered to prevent untoward developments in these patients.[82]

Righteous Usage

With the increase in treatment doses and duration of glucocorticoids, the probability of developing obvious side effects is also increasing. Therefore, short-term and low-dose treatments should be used. Zhao et al considered that a cumulative dose of methylprednisolone < 5 g and course of treatment < 30 days were associated with a relatively low risk of osteonecrosis.[76] According to Shanghai's experience in treating COVID-19 patients, the initial dose of methylprednisolone was 40–80 mg/day for 3 days which was gradually reduced to 20 mg/day. The total treatment duration was less than 7 days. The safety of this dose was satisfactory.[82] However, it has also been reported that even low-dose or short-term glucocorticoid therapy can cause FHN,[83] and the above protocol was not followed up. Yang et al found that intermittent treatment is less likely to cause osteonecrosis in mice than continuous dexamethasone treatment. This "steroid vacation" method may be used for reference in clinical use.[84]

Post Glucocorticoid-Use Plan

Diagnosis

Early diagnosis is necessary for timely treatment because the treatment options for advanced disease are limited and many patients of FHN are young and active individuals. Regular hip monitoring via magnetic resonance imaging (MRI) should be carried out in high-risk patients as it has a sensitivity of 93 to 100%.[85] Zhao et al emphasised the importance of regular screening via MRI. It was found that in 23 patients with a confirmed diagnosis of FHN, if MRI was only performed 2 to 3 months after hormone treatment, the diagnosis in 21 patients would be missed.[86] The reported onset time of FHN after glucocorticoid use is from 3 weeks to 3 months.[87,88] Diffusion-weighted MR images revealed that the diffusion of FHN was significantly enhanced, which can provide additional information to aid diagnosis.[89] Because the clinical manifestations appear later than the imaging examination findings, 78.82% of glucocorticoid-induced FHN patients complain of pain within 3 years after the commencement of steroid treatment and 10.41%, within 6 years or more. The diagnosis of glucocorticoid-induced FHN mainly depends on imaging examination. MRI should be performed 3, 6, and 12 months after steroid administration.[90] Ren et al suggested that ten main metabolites containing phosphatidylcholine are closely related to the early changes of steroid-induced FHN. If the clinical symptoms and imaging changes are not obvious, the ten metabolites can be used to monitor steroid-induced FHN 1 week later.[91] Sun et al pointed out that plasminogen activator inhibitor type 1 (PAI-1) is a sensitive haemogram for screening high-risk and susceptible populations.[92] In addition, serum levels of complement 3 (C3), C4, inter-alpha-trypsin inhibitor heavy chain H4, and α-2 macroglobulin may also be potential biomarkers for diagnosing FHN.[93] Wei et al found that serum miR-423-5p in patients with steroid-induced FHN was significantly increased, suggesting a potential role in its diagnosis.[94]

Treatment

Without treatment or intervention, FHN may become an irreversible process. Some medications such as lipid-lowering drugs, anticoagulants, vasodilators, and traditional Chinese medicines can reduce the chances of developing necrosis. Levodopa can reduce osteocyte apoptosis and promote the repair of necrotic zones by promoting the synthesis and release of insulin-like growth factor-1 (IGF-1).[95] Alendronate sodium can prevent and delay the progression of FHN by inhibiting the bone resorption capacity of osteoclasts and accelerating the apoptosis of osteoclasts.[96] Pilose antler extract can regulate the expression of 11β-hydroxysteroid dehydrogenase (11 β-HSD) in rabbits' femoral heads and osteoblasts, and promote the proliferation of osteoblasts.[97] Camporesi et al conducted a 7-year follow-up of patients with SANFH. The results showed that hyperbaric oxygen (HBO) treatment for 6 weeks significantly improved the clinical symptoms in SANFH patients. The HBO environment increases the oxygen concentration in the blood and reduces bone marrow oedema. In addition, it also promotes angiogenesis as well as the function of osteoblasts and osteoclasts and provides the necessary preconditions for the treatment of SANFH.[98] Koren et al considered HBO to be an effective method for the treatment of Association Research Circulation Osseous I and II (ARCO I and II) FHN in a study in which the patients were followed up for 11.1 ± 5.1 years.[99] But the high cost of HBO treatment may be an important prohibitive factor. Experiments on animals have revealed that pulsed electromagnetic field

stimulation can prevent SANFH in rats, and its mechanism may be related to the decrease in blood lipid levels and increase in transforming growth factor beta-1 (TGFβ-1) expression.[100] Ludwig et al reported that extracorporeal shock wave therapy (ESWT) of 1-year duration significantly reduced pain and improved hip joint function, which was suitable for patients with ARCO I to III FHN. ESWT induces neovascularization and improves the blood supply to the femoral head by enhancing the expression of vascular endothelial growth factor (VEGF) in the femoral head.[101] Liu et al retrospectively studied the long-term efficacy of combined therapy (alendronate sodium, ESWT, and HBO) in 37 patients with SANFH from 2003 to 2015. After 12 years of follow-up, it was found that comprehensive treatment can delay or prevent the development of SANFH after SARS. The combined treatment had different effects on FHN patients with different ARCO stages, and the greatest benefits were seen in patients with FHN ARCO I.[102] Xie et al found that although most patients received ESWT, HBO, or traditional Chinese medicine to promote local blood circulation, these methods had no obvious short-term effects on the recovery of the femoral head.[5] At present, significant progress has been made in the discovery of new ideas for treatment. Yang et al reported that the expression of gene *COL5A2* was low in patients with SANFH; hence, *COL5A2* may be a promising target in the treatment of SANFH.[103] Alpha-2-macroglobulin (A2MG) is involved in many mechanisms of SANFH including coagulation, hyperlipidaemia, and free radical and MMP degradation.[93] The results of real-time quantitative polymerase chain reaction (RQ-PCR) in a study showed that the level of serum A2MG in SANFH patients was significantly lower than that in the control group ($P < 0.05$). Immunohistochemical staining and Western blotting showed that the expression of *A2MG* in the necrotic area of patients with SANFH was significantly reduced ($P < 0.05$). Therefore, *A2MG* may become the new target in the treatment of SANFH.[104]

Conclusion

Even though there is a debate on the pros and cons of using steroid, from the perspective of orthopaedics, it is an indisputable fact that long-term and high-dose steroid use leads to ONFH. Therefore, we call for judicious use of corticosteroids in the treatment of COVID-19 patients and do not recommend it as a routine treatment. For patients who have received corticosteroid treatment, bisphosphonates, anticoagulants, vasodilators, and traditional Chinese medicine combined with ESWT, HBO, and other physical therapies can be considered. We reiterate the importance of regular screening in high risk patients, especially those on long-term steroids. MRI is the best tool for early detection of SANFH, and clinicians must take efforts to improve aware ness regarding the prevention of SANFH. A high index of suspicion is necessary for patients complaining of bone and joint pain at typical sites. Patients suspected of having SANFH should be referred to orthopaedic doctors in the early stages, and clinicians should try to delay the progression of osteonecrosis to prevent FHN from affecting the daily life of patients.

Abbreviations

COVID-19, coronavirus disease 2019; SARS, severe acute respiratory syndrome; ARDS, acute respiratory distress syndrome; CoV, coronavirus; SANFH, steroid-induced avascular necrosis of the femoral head; ONFH, osteonecrosis of the femoral head; IFN-γ, interferon gamma; TNF, tumor necrosis factor; IL-1, interleukin-1; IL-6, interleukin-6; BMSCs, bone marrow stromal cells; miR, microRNA; HBO, hyperbaric oxygen; ARCO, Association Research Circulation Osseous; ESWT, extra-corporeal shock wave therapy; MMP, matrix metalloproteinases.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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