A prolonged steroid therapy may be beneficial in some patients after the COVID-19 pneumonia

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**ABSTRACT**

**INTRODUCTION:** This report introduces two cases presenting absorption of considerable radiological changes in the course of the coronavirus pneumonia in patients treated with prolonged oral steroids.

**CASES:** The first case concerns a male receiving steroids only during hospitalisation in the Infectious Disease Hospital. After discharge, the patient experienced increasing dyspnoea resulting in hospitalisation in our Department of Lung Diseases. HRCT revealed progression of a bilateral, middle, and basal ground-glass opacity when compared to the examination performed at the early stage of the disease. The supplementary oxygen therapy and steroids were administered, followed by extended prednisone consumption up to 2 months after discharge. Follow-up HRCT revealed an almost complete absorption of the ground-glass opacity. The second case concerns a male treated with steroids only during hospitalisation in the Infectious Disease Hospital. Chest CT revealed widespread bilateral ground-glass opacities with consolidations. After discharge with no treatment, he suffered from severe dyspnoea and exercise intolerance, resulting in hospitalisation on the 7th day of home stay. Since then, a continued steroid treatment was administered resulting in a clinical, spirometric, and radiological improvement.

**CONCLUSIONS:** Based on these observations, patients after the COVID-pneumonia may derive benefits from a prolonged steroid treatment. Therefore, this class of medications should be considered in SARS-CoV-2 patients, especially in patients with persistent radiological changes and dyspnoea requiring the supplementary oxygen therapy. However, randomised controlled trials are required to establish guidelines for the steroid treatment in this group of patients.

**Introduction**

A proper approach to the discharge of patients with a history of the COVID pneumonia remains an unresolved matter. The essential quandary clinicians face is deciding whether ‘doing something is better than doing nothing’, with a simultaneous view to ‘doing nothing is better than doing something wrong’.

A coronavirus infection may proceed in three phases: the immunosuppressive state, normal immunity, and the hyperactivated immune response [1]. The ‘cytokine storm’ is responsible for the last phase and it might lead to the acute respiratory distress syndrome (ARDS) with a possible multiorgan failure (MOF). In post-mortem examinations, apart from diffuse alveolar damage (DAD) observed in the lung tissue, there are many organs affected by the coronavirus (like heart, kidney, liver, 2). As a result, it was hypothesised that the origin of the noticed disorders was caused by vascular dysfunction. These findings stay in line with the study presented by Borczuk et al. [3] pointing to vessels thrombi as one of the most frequent radiological abnormalities observed in this group of patients. Among others, tracheobronchial and alveolar inflammations (both acute and chronic), the presence of hyaline membranes, pneumocyte type II hyperplasia, alveolar wall inflammation, and finally organising pneumonia (OP) were observed – focal in 18% patients and diffuse in 16% patients. Polak et al. [4] divided COVID pathological changes into three patterns: epithelial, vascular, and fibrotic. The first one included DAD, denudation, and reactive pneumocyte atypia, while the vascular one, much more expressed in the coronavirus pneumonia than in ARDS or influenza,
involved microvascular damage, thrombi, and intra-alveolar fibrin deposits having the appearance of OP. The last phase with the fibrotic pattern appeared in the subsequent period of the coronavirus pneumonia.

A crucial study analysing the histological response to acute injury caused by SARS-CoV-19 was performed by Kory and Kanne [5]. Similarly to previous authors, they distinguished DAD, OP, or AFOP (acute fibrinous and organising pneumonia). In DAD a damage of layers of alveolar and epithelial cells is observed, resulting in the accumulation of fluid and proteins in the alveolus with two phenotypes: acute/exudative and organising/proliferative. This in turn leads to the formation of radiological abnormalities in CT scans. Progression of this stage is observed in certain patients involving fibrosis. In both OP and AFOP accumulated coagulative proteins and fibrin cause fibroblast activation and proliferation, eventually producing a connective tissue matrix.

Considering the fact that pulmonary fibrosis may be experienced by up to 17% of COVID patients [6], a crucial point is searching for treatment methods preventing the irreversible formation of the fibrous tissue.

Below we present two patients after the confirmed COVID-pneumonia who received exclusively short-term steroid treatments during hospitalisation in the Infectious Disease Hospital resulting in clinical decline and deterioration of radiological abnormalities in the chest CT after discharge.

Case report 1

A 67-year-old male with confirmed COVID-pneumonia was hospitalised for 2 weeks in the Infectious Disease Hospital and treated with 6 mg Dexamethasone per day. Chest CT revealed a bilateral, middle, and basal ground-glass opacity (GGO, Figure 1A). No steroid treatment was administered after discharge. In the following 2 weeks the patient experienced increasing dyspnoea resulting in hospitalisation in our Department of Lung Diseases. No sputum, fever, chest pain, or haemoptysis were observed. He worked as a priest. Neither in his medical history nor his family history had there been any previous lung diseases. He had never smoked and he was suffering from diabetes mellitus and hypertension. A physical examination, blood tests, and an arterial blood gas test revealed a respiratory failure with a partial pressure of capillary oxygen equal to 53 mmHg (PO₂) without carbon dioxide retention (pCO₂ = 34 mmHg) and discrete crackles over the lung fields. The patient was unable to perform spirometry. HRCT revealed deterioration of GGO when compared to the previous chest CT (Figure 1B). Considering the clinical picture and test results, the patient was treated with the supplementary oxygen therapy (OT, beginning with high flow, subsequently passive OT) and a steroid therapy including methylprednisolone (at the dose of 1000 mg per day for 4 days and 500 mg per day for 3 days) followed by prednisone (at the dose of 20 mg per day). After discharge, the patient continued the steroid therapy with prednisone (initially 10 mg, gradually reduced to 5 mg) for 2 months. HRCT performed 2 months after the steroid treatment revealed an almost complete GGO absorption (Figure 1C). Spirometry and the arterial blood gas test were within the norm (FVC = 94%pred., FEV₁ = 98%pred., PO₂ = 72 mmHg).

Case report 2

A 45-year-old male with a history of hypertension hospitalised in the Infectious Disease Hospital due to COVID-pneumonia for 3 weeks. Chest CT revealed a widespread, bilateral, ground-glass opacity with consolidations (Figure 2). During hospitalisation the patient was treated with steroids (dexamethasone at the dose of 6 mg per day), neither lung function tests nor chest X-ray were performed. After discharge, the patient received no recommendation to prolong the steroid therapy. On the 7th day of staying at home, he

Figure 1. CT scans of the 67-year-old patient suffering from the Covid-pneumonia, A – baseline, B – 1-month follow-up without steroid treatment, C – after 2 months of steroid treatment.
was admitted to hospital because of severe dyspnoea and exercise intolerance. Thereafter, the patient was again treated with steroids, receiving (dexamethasone at the dose of 6 mg per day), which was prolonged after discharge (prednisone 30 mg). Successively, the steroid treatment was continued for 2 months in the Lung Disease Outpatient Clinic (methylprednisolone at the dose gradually reduced, beginning with 24 mg). The chest X-ray performed on admission to the clinic revealed GGO in both mid and lower zones of the lungs, predominantly peripheral with some linear opacities and consolidations (Figure 3A). In spirometry no obstruction was observed; however, forced vital capacity was reduced (76%, SR −1.75). The arterial blood gas test turned out normal (pO₂ 83 mmHg). Figure 3B-3D presents an improvement in the follow-up chest X-ray and spirometric measurements in the presented case, subjected to a gradually reduced steroid treatment.

A similar trend to the presented cases was observed in all 18 patients after the COVID-pneumonia treated with steroids hospitalised in our Department between 16 September and 19 December 2020 with radiological abnormalities and dyspnoea requiring the supplementary non-invasive oxygen therapy.

Discussion

In the area of radiological abnormalities at an early stage of the COVID-pneumonia GGO, consolidation, a reticular pattern, interlobular septal or pleural thickening, bronchiectasis, and crazy paving are observed in

Figure 2. Chest CT of the 45-year-old patient suffering from the COVID-pneumonia.

Figure 3. Chest X-ray and spirometric measurements of the 45-year-old patient after COVID-pneumonia during a continued steroid treatment: A – baseline, B – after 10 days, C – after 1.5 month, D – after 5 months. FVC, forced vital volume.
the chest CT [6]. According to Shi [7] GGO changes may anticipate clinical signs and symptoms. Moreover, studies prove that over the course of a COVID-19 infection, the number of affected segments increases and simultaneously a replacement of GGO with consolidations and a mixed or reticular pattern is observed [7–9].

Based on numerous studies, Ojha systematises the knowledge about chest CT findings in the coronavirus disease and its follow-up [6]. It transpires that in most studies within a few to several days after a COVID-19 infection is confirmed, a follow-up CT scan revealed a progression of radiographic abnormalities, whereas merely four studies reported improvements. In a study on 67 COVID-19 patients with the OP pattern in their chest CT, in 47 patients residual lesions were observed, while in 20 patients a complete absorption was described [9]. The authors came to the conclusion that as the involvement of the lung lobes increases, increasing changes in CT scans are noticed with a lesser possibility of complete absorption.

According to EVMS [10] it is recommended to initiate the steroid therapy in the early pulmonary phase, including its intensification in case of the disease progression or entering into the late pulmonary phase. These findings are in concordance with a meta-analysis by WHO [11], reporting that corticosteroids are relevant in critical patients infected with SARS-CoV-19 irrespective of their gender, age, and symptoms with an acceptable safety profile. Consequently, WHO gave a strong recommendation to use corticosteroids in the treatment of patients with severe and critical COVID-19. These arrangements correspond to the EVMS statement based on the acronym MATHS+, which implies that intravenous methylprednisolone, alongside other drugs, such as ascorbic acid, thiamine, heparin, and others, is an indispensable part of the treatment approach to COVID [10].

The positive effect of steroids on the course of the COVID-disease is caused by its impact on the angiotensin-converting enzyme 2 (ACE2) and Interleukin 6 (IL-6). ACE2 has been proven to have a protective effect in the respiratory system, cardiovascular system, and kidneys [12]. The level of this enzyme, attached to the cell membranes and used to infect human cells, is reduced during the SARS-CoV-2 infection. Additionally, in COVID-19 patients, especially in severe cases, elevated levels of inflammatory cytokines including IL-6 were observed. It turns out that steroids, especially hydrocortisone, had a positive effect on the ACE2 expression and the IL-6 level reduction [12]. Successively, prednisolone, dexamethasone, and methylprednisolone also revealed a similar influence on ACE2 and IL-6. This study is an incontestable proof that medium-to-low-doses of glucocorticoids, by this mechanism, may have an impact on the protection of the respiratory and digestive systems in COVID-patients.

On the other hand, in a severe COVID-19 infection with MOF even high doses of steroids did not reduce mortality, while simultaneously increasing the risk of bacterial complications [1].

The previously mentioned radiological abnormalities, mostly described as GGO in the early stage of the disease, may progress after discharge. Spagnolo et al. [13] described a replacement of GGO zones with the fibrotic tissue even after the eradication of the coronavirus. This lung damage led to the development of the irreversible interstitial lung disease (ILD). Similarly, in the study of Dehan et al. [14] 3 weeks after discharge 45% of patients maintained GGO in the CT scan. In this research, the following discharge criteria were adopted: improvement in both radiological abnormalities and clinical symptoms (including absence of fever for at least 3 days), as well as two consecutive negative COVID-19 PCR tests. However, a strong limitation of this study is the absence of information about the treatment; therefore, it is impossible to assess factors which may have contributed to improvement in 53% of patients. The case presented by Jiangping demonstrated lung fibrosis in the early stage of the coronavirus disease, 18 days after discharge [15]. This research concluded that older patients with a severe COVID-19 infection, hospitalised for a longer period and with higher levels of the C-reactive protein, were particularly vulnerable to lung fibrosis measured by CT. Similar conclusions were made by Minhua, who observed that fibrosis occurred especially in patients with severe pre-existing conditions (such as diabetes, cardiac disease) and high inflammatory indicators [16]. Consequently, patients with pulmonary fibrosis presented a significantly longer stay in hospital. Moreover, the mentioned author established potential predictors of the pulmonary fibrosis manifesting itself in the course of the coronavirus pneumonia, including interstitial thickening, a coarse reticular pattern, an irregular interface and parenchymal band, of which the two latter predicted fibrosis at an early stage of the disease [16]. A longer follow-up of patients after the coronavirus pneumonia was performed by Zhao et al. [17], who observed that after 3 months in almost 71% patients, out of whom only nearly 13% had been treated with steroids, persistent radiological abnormalities and a reduced lung function tested were observed. In connection to this Raghu et al. [18] suggested
a prolonged follow-up of COVID-19 survivors of up to 36 months.

Studies agree as to the common CT-chest abnormalities in COVID patients presented as OP or AFOP [4,5]. Based on many years of experience in the treatment of OP disorders, it is proven that the corticosteroid therapy reduces symptoms and improves radiological abnormalities [5]. Having regard to the fact that a number of patients with an early stage of the coronavirus pneumonia present OP, AFOP, or both radiological changes in the CT scan, it seems reasonable to apply corticosteroids in the treatment of COVID-19. Indeed, the authors [5] emphasise a possibility of insufficient steroids dose contained in the RECOVERY trial protocol (which assumed 6 mg dexamethasone daily for up to 10 days, a maximum of 14 days), taking into account the fact that the OP treatment very often requires higher doses (about 40 mg prednisone) in a longer term (up to 6 months). Therefore, the corticosteroid dosing as recommended in the cryptogenic organising pneumonia (COP) treatment should be considered, unless adverse reactions are presented.

In accordance with George et al. [19], who presented the discharge criteria for patients at the highest risk of coronavirus pneumonia complications, patients with OP and/or an early stage of pulmonary fibrosis are supposed to be treated with corticosteroids with a gradual dose reduction. In the case of the persistent evidence of ILD in the CT scan, these patients should be referred to pulmonary specialists. An important part of the treatment is also pulmonary rehabilitation, already effectively implemented in patients with chronic lung diseases.

Considering several similarities between post-COVID-19 changes and post-ARDS changes, until now only a short course of steroids has documented effects on survival in patients with ARDS [20]. However, there are a variety of causes besides viral infections leading to ARDS [21]. As regards the Covid-19 pneumonia, ARDS concerns below 5% of patients [22,23]. To date, no prospective study has provided evidence for the superiority of a prolonged steroid treatment in patients with post-ARDS. Therefore, a prolonged steroid treatment in COVID-19 associated ARDS may not be reasoned. Furthermore, in the presented cases treated in our Department with a prolonged steroid therapy and with high flow and non-invasive ventilation, there were no patients after ARDS with post-COVID-19 pulmonary fibrosis.

Besides the persistence of radiological abnormalities, lung function tests are also impaired after the COVID-19 infection. In the study of Dongqing, 2 weeks after discharge in patients with the coronavirus pneumonia, the inspiratory vital capacity (IVC) was reduced in almost 89% of severe cases and 79% of non-severe patients [24]. In the study of Xiaoneng almost a half of the patients presented a reduced diffusing capacity for carbon monoxide (DLCO) and one quarter had a decreased forced vital capacity (FVC) [25]. As might be expected, these limitations were more pronounced in severe cases. We may suppose that pulmonary fibrosis and lung function impairments may be a significant problem affecting the elderly with the history of the coronavirus pneumonia, impairing the lung function and reducing the quality of life [13].

Conclusion
Several radiological abnormalities (GGO, consolidations, perhaps crazy-paving pattern) in the course of COVID-pneumonia are potentially reversible and may decrease due to the steroid treatment. Based on available studies and the authors’ own experience demonstrated with the presented cases, we conclude that patients after the COVID pneumonia requiring hospitalisation due to dyspnoea and/or the non-invasive ventilation therapy may derive benefits from a prolonged steroid treatment. In this paper, most patients presented GGO and consolidations in chest radiographs that absorbed during the steroid treatment. It should be noted, however, that in the mentioned cases, there were no patients after ARDS with post-covid pulmonary fibrosis. Apparently, steroids will be insufficient to reduce honeycombing fibrosis, traction bronchiectasis, and architecture distortion. Nonetheless, in the presented cases steroids administered in a prolonged therapy appeared to prevent lung fibrosis. Consequently, in our opinion, the steroid therapy is worth considering in SARS-CoV-2 patients, especially in patients with persisting radiological changes and dyspnoea requiring the supplementary non-invasive oxygen therapy. However, randomised controlled trials are required to establish guidelines for the steroid treatment in this group of patients.

Disclosure of potential conflicts of interest
No potential conflict of interest was reported by the author(s).

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