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Oseltamivir and baloxavir: Dual treatment for rapidly developing ARDS on a patient with renal disease

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ABSTRACT

Influenza is an annual epidemic disease that in severe cases can lead to the development of ARDS. Current practice recommends the routine use of neuraminidase inhibitors with emerging evidence for the use of endonuclease inhibitors. We present the case of a 22-year-old female with diabetes and IgG4 tubulo-interstitial nephritis that developed rapidly progressive ARDS from influenza infection requiring ventilatory support and extra corporeal oxygenation in which oseltamivir and baloxavir were used in combination. Patient oxygen requirements and imaging improved significantly after treatment initiation, leading to an overall short period of therapy. We present the first case of a patient treated with this combination in the context of chronic kidney disease.

Introduction

Influenza represents an annual global health problem, with such an impact that the CDC estimates between 23,000 and 61,000 deaths per year from 2015 to 2019 in the US alone [1]. The spectrum of disease varies and can range from a febrile upper respiratory disease to Acute Respiratory Distress Syndrome (ARDS), the latter often requiring mechanical ventilation. Current guidelines recommend that patients requiring hospitalization for influenza-related illness should receive oseltamivir, regardless the time of symptoms onset. Duration of treatment should be decided on a case-by-case basis [2]. The recommendations are based on the available evidence that neuraminidase inhibitors (NAI) have been shown to decrease mortality, length of stay and complications. However, a new family of influenza drugs has been approved for use, namely endonuclease inhibitors (EI), represented by baloxavir marboxil.

Currently, there are ongoing trials regarding the use of both NAIs and EIs concomitantly in patients with severe influenza, but they exclude patients with renal disease [3]. The case described below represents a patient with severe renal impairment and severe influenza related illness in which both medications were utilized.

Case

The patient is a 22-year-old female, with a past medical history of asthma, insulin-dependent diabetes and recently diagnosed IgG4 tubulointerstitial nephritis (IgG4 TIN), who presented with cough and congestion of 3 days duration. She tested positive for influenza B, her chest x-ray on admission showed bilateral interstitial infiltrates (Fig. 1A), and she was started on renally-adjusted oseltamivir (CrCl 14 mL/min). Over the next 48 h, due to increasing oxygen demand and impending respiratory failure the patient was placed on mechanical ventilation (Fig. 1 B) and the oseltamivir dose was doubled. Echocardiography showed normal left side pressures. Due to the continuous decline of her respiratory condition, the patient was started on extracorporeal membrane oxygenation (ECMO) on the fourth day of hospitalization (Fig. 1 C). Baloxavir was then added at a dose of 40 mg every 72 h for three doses, methylprednisolone was given for 4 days with a cumulative dose of 1125 mg, started on the fourth day of hospitalization. Further work up for bacterial and fungal pulmonary infections, including bronchoalveolar lavage, was negative. Chest x rays taken 48 h post initiation of baloxavir showed significant improvement of the bilateral pulmonary infiltrates and after another 48 h the patient was taken off ECMO and was extubated three days afterwards (Fig. 1 D). Subsequently, she was discharged home.

Discussion

Influenza B is an Orthomyxovirus that only infects humans. The virus enters the epithelial lining using its hemagglutinin and subsequently new viral particles are assembled and released

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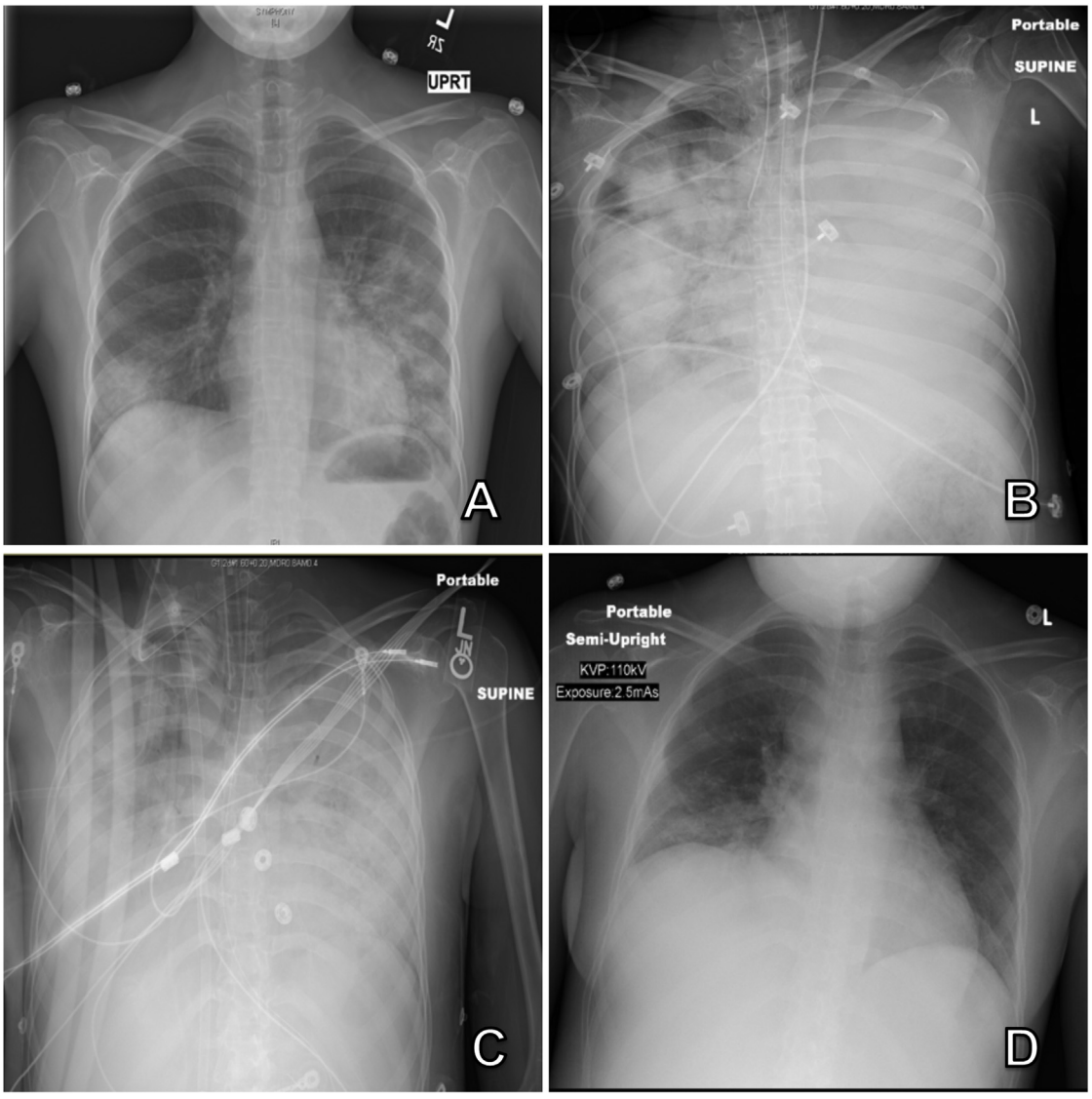

Fig. 1. (A) Admission chest x-ray with bilateral pulmonary infiltrates mainly on bases, (B) Progression of bilateral infiltrates at the time of intubation, (C) Extra corporeal oxygenation instauration, (D)Extubated and decannulated patient 7 days after initial imaging.

through the action of neuraminidase. The virus replicates along the epithelial lining of the respiratory tract, where it induces an inflammatory response, resulting in cellular death and congestion of the local vasculature. Altogether, these changes correlate with the clinical manifestations of tracheobronchitis and pharyngitis [4]. Once it affects the lungs, further changes such as alveolar necrosis, edema and the formation of hyaline membranes can occur. If the latter compromises a significant amount of pulmonary parenchyma, ARDS ensues [4,5].

Guidelines for hospitalized patients with influenza recommend the use of NAIs, which target neuraminidase, halting viral replication and decreasing the length of symptoms and mortality. Oseltamivir, zanamivir and peramivir are the NAIs approved for influenza treatment in the US and clinical efficacy seems comparable between them but previous attempts to use them in combination have not shown additional benefit [6–8]. Immunocompromised patients seem to be at increased risk of infection with NAI-resistant strains and also to develop severe disease [9]. Our diabetic patient was on chronic oral prednisone for her autoimmune nephropathy developed ARDS within 72 h from admission and required maximal ventilator settings, despite being on oseltamivir for three days. The use of zanamivir, was contraindicated because of the underlying asthma and IV peramivir was not available.

Baloxavir is a new antiviral medication with a mechanism of action of inhibiting the endonuclease activity of the polymerase acidic (PA) protein, part of the viral RNA polymerase complex required for viral gene transcription [10]. A recent study comparing the use of baloxavir to oseltamivir in hospitalized patients with influenza, showed increased resolution of hypoxemia as well as a

shorter duration of hypoxia in the baloxavir [11]. However, this study did not specify the severity of the disease. Currently, there is an ongoing trial comparing the efficacy of baloxavir and oseltamivir to baloxavir and placebo in patients with severe disease [ClinicalTrials.gov Identifier: NCT02954354]. Our patient was not eligible due prior exposure to oseltamivir and chronic kidney disease.

ARDS is a clinical entity characterized by progressive bilateral pulmonary infiltrates that cannot be fully explained by cardiac disease or volume overload. Despite advances on the understanding of this condition, mortality remains significant [12]. Management involves lung-protective ventilation, prone positioning, corticosteroids, paralytics and ECMO. The use of corticosteroids is controversial, with data showing that high dose of steroids fails to improve mortality and might cause harm [13,14]. On the other hand, the CESAR trial showed improved survival on ECMO compared to conservative management with medium duration of cannulation of 9 days [15]. Our patient was started on high dose methylprednisolone along with ECMO support, given the improvement on her respiratory status she was decannulated after 4 days.

This is a case that depicts a rapidly developing ARDS caused by influenza, requiring invasive ventilation and the use of ECMO as supportive measurements. Baloxavir was added to oseltamivir with prompt imaging improvement and an overall short period of intubation and cannulation. While steroid use could be argued to play a role in her improvement, evidence shows that high dose steroids do not benefit this population. Given the acceptable safety profile of both medication and the lack of interaction between them, it could be considered when treating patients at risk for resistant strains and severe disease. After reviewing the literature, this is the first case of dual therapy with these drug families in a patient with poor renal function.

Author statement

All the authors from this manuscript are in agreement and have no further declarations. We submit the reviewed manuscript and thank you review it.

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