Multiple drugs

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Lack of efficacy and off-label use: 3 case reports

A case series described 3 patients including 2 women and 1 man aged 42–52 years old, who exhibited lack of efficacy during off-label treatment with levofloxacin, celecoxib, convalescent-anti-sars-cov-2-plasma, dexamethasone or prednisone for COVID-19 pneumonia [*not all routes and dosages stated*].

Case 1: A 42-year old woman, who was obese and an ex-smoker had history of bacterial pneumonia. In November 2020, she was diagnosed with COVID-19 pneumonia and received off-label treatment with oral prednisone 1 mg/kg and celecoxib. She also received unspecified low-molecular weight heparin (LMWH) and paracetamol. Despite prednisone and celecoxib therapy, 2 days later, she developed worsening dyspnoea and was admitted to the emergency department (ED). She had developed hypoxaemia thus high-flow oxygen therapy and continuous positive airway pressure (CPAP) were started. Then, off-label IV dexamethasone was initiated for COVID-19 pneumonia. Despite dexamethasone therapy, respiratory parameters did not improve and she was transferred to the ICU, where orotracheal intubation (OTI) was performed. Due to the need of extra-corporeal membrane-oxygenation (ECMO) support, she was then transferred to the tertiary care hospital. In ICU, she was treated with anticoagulant therapy including bivalirudin and unspecified antithrombin, prophylactic unspecified wide-spectrum antibiotic and off-label IV methylprednisolone. Due to the progressive stabilisation of respiratory function on ECMO support, she was extubated and given oral feeding. On 04 December 2020, a second chest CT scan showed a worsening interstitial thickening. Due to considerable deterioration of the lung tissue, she was started on oral nintedanib 150mg twice a day through compassionate use (off-label use) for COVID-19 pneumonia. In the next few days, clinical improvement occurred. The favorable disease course allowed for the suspension of ECMO, while steroid therapy was shifted to off-label oral methylprednisolone. A chest CT scan performed at day 27 of therapy showed a dramatic improvement in lung parenchymal alterations. At day 56 of nintedanib treatment, she was discharged from the hospital, although still necessitating oxygen during exercise. Nintedanib was withdrawn after 67 days of therapy. A chest CT scan performed at follow-up showed further improvement of lung parenchyma and reduction of residual lung damage.

Case 2: A 48-year old man, who was obese and an ex-smoker had history of arterial hypertension. He had been receiving therapy with thiazide, angiotensin II receptor blocker and statin [*drugs unspecified*]. In November 2020, he was diagnosed with COVID-19 pneumonia and received off-label treatment with oral prednisone 25mg. He also received unspecified low-molecular weight heparin (LMWH). A few days later, despite prednisone therapy, he developed worsening dyspnoea and was admitted to the emergency department (ED). He had developed hypoxaemia thus high-flow oxygen therapy and continuous positive airway pressure (CPAP) were started. Then, off-label IV dexamethasone was initiated for COVID-19 pneumonia. Despite dexamethasone therapy, respiratory parameters did not improve and he was transferred to the ICU where initial CPAP and prono-supination cycles were soon followed by orotracheal intubation (OTI) and mechanical ventilation. In ICU, he was treated with unspecified antibiotic for prophylaxis. Chest CT scan showed extensive lung parenchymal alterations with widespread consolidations and signs of initial evolution toward lung fibrosis. Due to the need of extra-corporeal membrane-oxygenation (ECMO) support, he was then transferred to a third-level hospital. He was treated with off-label IV methylprednisolone for COVID-19 pneumonia, anticoagulant therapy including bivalirudin and antithrombin-III, and unspecified antibiotics for prophylaxis. He was progressively weaned from ventilator support and finally extubated on 28 December 2020, but continued with ECMO support. As lung function did not improve significantly since extubation, oral nintedanib 150mg twice a day was started through compassionate use (off-label use) for COVID-19 pneumonia resulting in progressive improvement. He was discharged from ICU and transferred to the rehabilitation unit. Nintedanib treatment was discontinued after 71 days. A chest CT scan performed one month after nintedanib withdrawal revealed a consistent improvement.

Case 3: A 52-year old woman had history of autoimmune thyroiditis, hypertension, hypercholesterolaemia, obesity and anxiety. She was on chronic therapy with levothyroxine and unspecified statin. In November 2020, she as diagnosed with COVID-19 pneumonia and received off-label treatment with levofloxacin. Despite, levofloxacin therapy no improvement was noted. Due to worsening lung function, she was admitted to the emergency department (ED) and received off-label IV dexamethasone and convalescent-anti-sars-cov-2-plasma for COVID-19 pneumonia without benefit. She was thus transferred to ICU and orotracheal intubation (OTI) was performed. She received unspecified low-molecular weight heparin (LMWH). For persisting severe respiratory dysfunction, she was transferred to our third level hospital and started extra-corporeal membrane-oxygenation (ECMO) support. She was treated with anticoagulant therapy including bivalirudin and antithrombin-III), off-label IV methylprednisolone for COVID-19 pneumonia, unspecified prophylactic antibiotic therapy, and unspecified anti-hypertensive therapy to control blood pressure. She also necessitated percutaneous tracheostomy for mechanical ventilation. In response to maximal treatment, the respiratory function and her general clinical condition became progressively stable, allowing for OTI removal. On 22 December 2020, a chest CT scan revealed diffuse bilateral GGO. The same day, she was started on oral nintedanib 150mg twice a day was started through compassionate use (off-label use) for COVID-19 pneumonia resulting in rapid improvement. Then, she received off-label oral methylprednisolone for COVID-19 pneumonia. At hospital discharge, she was eupneic on room air at rest, while still necessitating oxygen support during exercise. Nintedanib was discontinued after 79 days of therapy. A chest CT scan performed 34 days after drug discontinuation showed the progressive reduction of GGO.

Bussolari C, et al. Case Report: Nintedaninb May Accelerate Lung Recovery in Critical Coronavirus Disease 2019. Frontiers in Medicine 8: 766486, 28 Oct 2021. Available from: URL: https://journal.frontiersin.org/journal/medicine

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