Multiple drugs

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Various toxicities: 4 case reports

In a case series, 4 men aged from late 50s–late 70s [*exact ages not stated*] in the Netherlands who were diagnosed with COVID-19 between December 2020 and May 2021 were described, who developed COVID-19 associated mucormycosis (CAM), pulmonary aspergillosis or experienced worsening mucormycosis during off-label treatment with tocilizumab, prednisolone, dexamethasone or prednisone for COVID-19 infection. Additionally, the patients exhibited lack of efficacy during treatment with amphotericin B liposomal, isavuconazole, posaconazole or interferon gamma for CAM [*routes not stated; not all dosages not stated*].

Case 1: The man in his mid-60s, was admitted to the intensive care unit (ICU), 8 days after onset of COVID-19 symptoms. He started receiving off-label single dose of tocilizumab 600mg, on the first day of ICU admission. He also started receiving off-label dexamethasone 6mg/day, from day 1 to day 10 of ICU admission. On day 9 of ICU admission, he developed bilateral consolidations. On the same day, oropharynx and sputum cultures were positive with *Rhizopus microspores*. A bronchoscopy was performed and bronchoalveolar lavage (BAL) showed R. microspores. From day 10 to day 12, he started receiving off-label prednisolone 60mg/day. Based on the results of investigations, he was diagnosed with CAM, 22 days after COVID-19 diagnosis. Initially, he was treated with voriconazole. Subsequently on day 13, he started receiving amphotericin B liposomal. However, chest CT revealed clinical deterioration and worsening consolidations (lack of efficacy). On day 19, he also started receiving posaconazole. At the time of writing this report, he continued his antifungal treatment and continued mechanical ventilation in the ICU. The CAM was attributed to tocilizumab and dexamethasone and worsening mucormycosis to prednisolone.

Case 2: The man in his late-50s, was admitted to the ICU, 6 days after onset of COVID-19 symptoms. He started receiving off-label single dose of tocilizumab 600mg, on day 1 of ICU admission. He also started receiving off-label dexamethasone 6mg/day, from day 1 and day 10 of ICU admission. On day 6 in the ICU, he was diagnosed with pulmonary aspergillosis and he was treated with voriconazole. On day 9 of ICU admission, sputum culture was positive for *Lichtheimia ramose* consistent with the diagnosis of CAM. He started receiving amphotericin B liposomal and posaconazole. CAM was diagnosed, 17 days after COVID-19 diagnosis. On day 21 of ICU admission, his clinical condition deteriorated. Thereafter, he died (lack of efficacy), 27 days after COVID-19 diagnosis. An autopsy was not performed. The CAM and pulmonary aspergillosis was attributed to dexamethasone and tocilizumab.

Case 3: The man is his late-60s, with a history of chronic lymphocytic leukaemia, diabetes mellitus and obesity, was admitted to the ICU for mechanical ventilation due to progressive respiratory failure. On day 1 of ICU admission, he received off-label single dose of tocilizumab 800mg. He started receiving off-label dexamethasone 6mg/day, from day 3 to day 7 of ICU admission. He also received off-label prednisone. On day 10 of ICU admission, acute-onset kidney failure and respiratory deterioration occurred. He was diagnosed with pulmonary aspergillosis and he was treated with voriconazole and micafungin, from day 9 to day 21 of ICU admission. On day 21 of ICU admission, sputum culture showed *Rhizopus microspores* consistent with the diagnosis of CAM. He started receiving isavuconazole, from day 21 to day 24 of ICU admission. A subsequent lung biopsy was negative. On day 30 of ICU admission, he discontinued voriconazole. Thereafter, amphotericin B liposomal and interferon gamma was added to the antifungal regimen. However, repeated CT scans showed progression of pulmonary lesions and dissemination to the kidneys indicating disseminated mucormycosis (lack of efficacy). Microscopy revealed non-septate hyphae in his urine. Subsequently, 46 days after COVID-19 diagnosis, he died. Autopsy confirmed disseminated mucormycosis. The CAM and pulmonary aspergillosis were attributed to tocilizumab, prednisone and dexamethasone.

Case 4: The man is his early 70s had been receiving off-label dexamethasone for COVID-19. He was re-admitted to the hospital for treatment of a cerebrovascular stroke causing left-sided paralysis, within a month following discharge. His diabetes mellitus was poorly controlled. He presented with fever, swelling of his right eye and loss of vision caused by extensive sinusitis with intracranial necrosis and infarction. Orbital pus was positive for *Rhizopus arrhizus* consistent with the diagnosis of CAM. He started receiving amphotericin B liposomal, isavuconazole and interferon gamma for 7 weeks. Surgical debridement was performed. However, the treatment were not successfully to contain the infection (lack of efficacy). Subsequently, he died, 129 days after COVID-19 diagnosis. The CAM was attributed to dexamethasone.

Buil JB, et al. Case series of four secondary mucormycosis infections in COVID-19 patients, the Netherlands, December 2020 to May 2021. Euro Surveillance 26: No. 23, 10 Jun 2021. Available from: URL: http://doi.org/10.2807/1560-7917.ES.2021.26.23.2100510

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