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Editorial Comment

EDITORIAL COMMENT

Therapeutic dilemmas in dialysis patients hospitalized for COVID-19: balancing between nihilism, off-label treatment and side effects

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ABSTRACT

Avoiding the use of drugs in patients with a glomerular filtration rate (GFR) <30 mL/min/1.73 m^2 is due to the exclusion of this group of patients from many clinical trials. However, in view of the widespread COVID-19 pandemic and the need to treat all patients, including those with renal failure, the World Health Organization points out in the Solidarity trial the need for the inclusion some patients with kidney failure and recognizes the urgent need for trials/studies in patients with coronavirus disease 2019 (COVID-19) with lower GFR. It is well known that the therapeutic goal to treat patients with renal failure, acute kidney injury or on maintenance dialysis is complicated by pharmacokinetics, drug interactions and extracorporeal therapies. In patients with COVID-19 and impaired kidney function, the role of nephrologists is crucial in order to draw a balance between nihilism and benefits or potentially harmful effects of current available treatments. The potential use of European Medicines Agency recommended remdesivir and dexamethasone for COVID-19 among dialysis patients are discussed.

Keywords: AKI, chronic hemodialysis, COVID-19, dexamethasone, remdesivir, SARS-CoV-2

To date, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), known as coronavirus disease 2019 (COVID-19), is the most difficult global therapeutic problem for clinicians. In patients with COVID-19, the prevalence of renal disease on admission and acute kidney injury (AKI) during hospitalization is high [1]. Another group with a relatively high incidence of COVID-19 and associated high in-hospital mortality is patients with end-stage kidney disease (ESKD) on maintenance hemodialysis. According to the latest European Renal Association COVID-19 Database (ERACODA) report, their 28-day probability of death is 25% [2]. The particular risk of hemodialysis patients to contract SARS-Co-V-2 infection is due to frequent exposures to other patients and staff at dialysis centers [3].

On 1 December 2020, the European Medicines Agency recommended only remdesivir (RDV) and dexamethazone for the treatment of COVID-19 in patients with pneumonia who require supplemental oxygen [4]. RDV is a nucleotide analogue that inhibits viral RNA polymerase, and dexamethasone is a steroid intended to control the inflammatory consequences of infection. Unfortunately, according to product prescription guidance, RDV is not recommended for COVID-19 in patients with renal failure [glomerular filtration rate (GFR) <30 mL/min/1.73 m^2], given the absence of safety data in this population [5]. RDV is a prodrug, predominantly metabolized by hepatic enzymes with hydrolase activity. Pharmacokinetics of RDV has not been evaluated in patients with renal impairment. Notably, nephrotoxic

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adverse events have not been demonstrated in placebo-controlled trials with RDV [6]. The intravenous form contains the carrier sulfobutylether-β-cyclodextrin (SBECD), a cyclic oligosaccharide that is predominantly excreted through glomerular filtration. Animal studies have shown liver necrosis and renal tubule obstruction linked with SBECD at doses 50- to 100-fold higher than expected for a 5- to 10-day RDV course [7]. Each 100 mg of lyophilized powder and solution of RDV contains 3 and 6 g of SBECD, respectively, which is far below the maximum recommended safety threshold dose of 250 mg/kg/day. Additionally, SBECD is effectively removed by continuous renal replacement therapy and a 4-h hemodialysis session removes almost half of the accumulated SBECD to the limits generally considered safe [8]. Accumulation of sulfobutylether-β-cyclodextrin may occur in patients who discontinue dialysis without renal improvement. The recommended 5–10 days administration with RDV and relatively low concentrations of SBECD additionally reinforced by dialysis suggest that the benefits of therapy may outweigh the risks. Elevated liver enzymes (mainly alanine aminotransferase) attributed to the use of sulfobutylether-β-cyclodextrin in patients with renal insufficiency were rare and transient [9, 10]. It has been suggested that RDV may be used in dialysis patients with close monitoring of liver enzymes [11].

The currently published series of 46 AKI patients with COVID-19 on maintenance hemodialysis clearly indicates good RDV tolerance at standard doses [12]. Slightly elevated transaminases (mild liver dysfunction) at baseline were clinically irrelevant, did not lead to early discontinuation of therapy and improved after treatment termination. Twenty-four patients (52.2%) with ESKD/AKI treated with RDV were discharged from the hospital. A recently published report on the plasma concentration of RDV and its metabolite (GS-441524) in three hemodialyzed patients suggests that a 5-day course of RDV was associated with pre- and postdialysis concentration fluctuations [13]. RDV in general was well tolerated and GS-441524 was removed by hemodialysis. Posthemodialysis concentrations were 45–49% lower than the most recent prehemodialysis measurement.

All above mentioned studies suggest that patients without underlying liver disease, who are expected to undergo continuous or intermittent dialysis or those with expected transient AKI may be the best candidates to receive RDV. Ultimately patients or their legal representatives should provide written informed consent for use of RDV in this emergency setting despite the lack of safety data in patients with an eGFR <30 mL/min/1.73 m^2 [11].

As a result of the Randomised Evaluation of COVid-19 thERapY (RECOVERY) trial, dexamethasone is the second recommended drug for patients with COVID-19 who require supplemental oxygen [14]. It reduced the risk of death by ~30% for people on ventilators and by ~20% for people who needed supplemental oxygen. Other corticosteroids, such as prednisone, methylprednisolone or hydrocortisone, may be used if dexamethasone is not available. Dexamethasone and other corticosteroids may be harmful if given for less severe COVID-19 infection, due to side effects and prolonged clearance of viruses. Our experience with dexamethasone comes from the treatment of dialysis-dependent patients with myeloma. It should be given with caution, especially in anuric patients, due to rapid weight gain with fluid retention. Therefore the frequency of dialysis cannot be reduced, but rather is increased (e.g. 4 times per week), in those with fluid accumulation. Other side effects include hypertension and especially gastritits, with a higher risk of ulceration and bleeding in patients with COVID-19 put on concomitant prophylactic anticoagulation (own observations).

Avoiding the use of drugs in patients with a GFR <30 mL/min/1.73 m^2 is due to the exclusion of this group of patients from many clinical trials. However, in view of the widespread COVID-19 pandemic and the need to treat all patients, including those with renal failure, the World Health Organization points out in the Solidarity trial the need for the inclusion of patients with kidney failure and recognizes the urgent need for trials/studies in patients with COVID-19 who have lower GFR [15]. Recently the ERA-EDTA council and ERACODA Working Group issued an important document calling on researchers to not exclude dialysis patients from clinical trials focused on COVID-19 and to pay attention to vaccine doses/schemes, as the immune response can be different than that of the general population [16].

In conclusion, it is well known that the therapeutic goal to treat patients with renal failure, AKI or on maintenance dialysis is complicated by pharmacokinetics, drug interactions and extracorporeal therapies. However, some toxicities (RDV carrier as example) are better controlled with dialysis treatment. Thus there is no doubt that in patients with COVID-19 and impaired kidney function, the role of nephrologists is crucial in order to draw a balance between nihilism and the benefits or potentially harmful effects of available treatments.

CONFLICT OF INTEREST STATEMENT

None declared.

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