Liver and kidney function in patients with Covid-19 treated with remdesivir

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What is already known about this subject?

- Nephrotoxicity and hepatotoxicity are reported as adverse events during randomized controlled trials of remdesivir treatment in patients with Covid-19.
- Patients with an impaired kidney or liver function were excluded from the trials.
- Impaired kidney or liver function are stated as contra-indication for treatment with remdesivir.

What this study adds:

- This real-world population of patients with Covid-19 includes 20% of patients who have been excluded from clinical trials based on their renal- or liver function.
- Hepatoxicity and nephrotoxicity of remdesivir are mostly mild, and severe adverse events are limited.
- Contra-indications based on kidney- and liver function should not be absolute if functions are monitored regularly.

Abstract

For the treatment of Covid-19 patients with remdesivir, poor renal- and liver function were both exclusion criteria in randomized clinical trials (RCTs) and contra-indication for treatment. Also, nephrotoxicity and hepatotoxicity are reported as adverse events. We retrospectively reviewed renal- and liver functions of covid-19 patients who received remdesivir in the 15 days after treatment initiation. Approximately 20% of the patient population met RCT exclusion criteria. In total, 11% of the patients had a decrease in estimated glomerular filtration rate larger than 10 ml/min/1.73m2. Also, 25% and 35% had increased alanine transaminase and aspartate transaminase levels, respectively. However, serious adverse events were limited. Therefore, contra-indications based on kidney- and liver function should not be absolute for remdesivir treatment in patients with Covid-19 if these functions are monitored regularly.

Introduction

Nephrotoxicity and hepatoxicity were reported as adverse drug events in patients with coronavirus disease 2019 (Covid-19) treated with remdesivir (1), and included as a contra indication for treatment in the summary of product information (1, 2). Also, Covid-19 patients with impaired kidney- (estimated glomerular filtration range [eGFR] <30 or <50 ml/min/1.73m2) or liver function (alanine transaminase [ALT] or aspartate transaminase [AST] five times upper limit of normal [ULN]; ALT male: 45 U/l, female: 35 U/l; AST male: 35 U/l, vrouw: 30 U/l]) were excluded from randomised clinical trials (RCTs) with remdesivir (1, 3, 4). We briefly report changes in renal- and liver functions during treatment with remdesivir in a Covid-19 patient population, regardless of the initial laboratory values. Hereby, additional information was obtained about the incidence and severity of nephro- and hepatotoxicity due to remdesivir treatment in clinical practice.

Patients and methods

We included hospitalized (Leiden University Medical Center, The Netherlands) adult patients on a regular ward with oxygen suppletion who started 5-day remdesivir treatment (intention to treat) between August 17 and November 4, 2020. All patients had a severe acute respiratory syndrome

coronavirus-2 infection confirmed by polymerase-chain-reaction. Per patient, age, sex, remdesivir prescription data, and laboratory parameters (eGFR, AST, ALT) were extracted from the electronic health record using CTcue text mining software (CTcue B.V., Amsterdam, The Netherlands). We determined renal- and liver function at start of remdesivir, and change of parameters in a follow-up period of 15 days after remdesivir treatment initiation, both per patient and as mean change per day. Adverse event classification was according to the Common Terminology Criteria for Adverse Events version 5.0. Patients were excluded if no laboratory measurements were available.

Results

In total, 103 patients were included in this study, of whom at least one of the laboratory measurements was available, the majority of them being male (68%), and the median (interquartile range, IQR) age was 64 (56 – 75) years.

Figure 1 shows the change in eGFR, AST and ALT compared to the baseline measurements per individual patient and mean change per day after remdesivir initiation.

At start of treatment, the median baseline eGFR in 95 patients was 74.0 (IQR 54.5 – 87.0) mL/min/1.73m^2. In total, ten (10.5%) patients had a decrease in eGFR of more than 10 ml/min/, 1.73m^2; the maximum decrease in eGFR was 21 mL/min/1.73m^2. Of all patients, 21 (22.1%) started treatment with an eGFR below the trial exclusion limit of 50 ml/min/1.73m^2 and two (9.5%) had a decrease in eGFR of more than 10 ml/min/1.73m^2 (figure 1A).

The baseline median AST was 40.0 (IQR 27.0 – 58.5) U/L in 81 patients, of which 33 patients started with a normal AST, 48 an AST above ULN, which includes four patients out of the trial exclusion limit of 5x ULN. After start with remdesivir, thirteen patients (39%) with baseline AST in normal range had an increase in AST > ULN (grade 1 adverse event), one patient (3%) had an increase in AST above 3x ULN (grade 2 adverse event) and one patient AST 5x >ULN(grade 3 adverse event). Of the 48 patients where baseline was initially above ULN, two of them met the exclusion limit, five (10.4%) had an increase of 1.5x baseline (grade 1 adverse event). The maximum increase in AST was 147 U/L (figure 1B).

The baseline median ALT was 32.0 (IQR 22.0 – 55.8) U/L in 95 patients, 54 started remdesivir treatment with a normal ALT and 41 with ALT above ULN, of which two patients with ALT > 5x ULN. In total 19 (35%) of patients starting with a normal ALT had an increase of ALT >ULN (grade 1 adverse event), three patients (6%) had ALT > 3x ULN (grade 2) and one patient had AST > 5x ULN (grade 3). Nine patients (22%) that started remdesivir treatment with ALT above ULN had an increase in ALT >1.5x baseline (grade 1), however in none of them >3.0x baseline (grade 2) was reported. The maximum increase in ALT was 210 U/L (figure 1C).

Discussion and conclusion

Overall, in 103 hospitalized Covid-19 patients who received a maximum of 5 days remdesivir treatment, no severe nephrotoxicity and in two patients grade 3 hepatotoxicity was found in the first fifteen days after treatment initiation.

The incidence of decreased glomerular filtration rate was comparable data reported in the RCTs last year (3, 4). A quarter and a third of our population had AST and ALT elevation, which is more than the adverse events reported in RCTs, 3.4-5% and 2.3%-6%, respectively. However, Beigel et al. only reported adverse events of grade 2 or higher; Wang et al. and Goldman et al. did not specify the grade of adverse events included in the study (1, 3, 4). Most of the liver transaminase elevation in patients in our study was mild, of grade 1. Only 1% showed grade 3 elevation, whereas Goldman et al. reported grade 3 and 4 adverse events in 2-6% of the patients (4). None of the patients that started with transaminases above ULN, including patients meeting exclusion criteria, had grade 2 or higher transaminase elevation.

In a real-world population, we found that the incidence of decreased eGFR during treatment with remdesivir was comparable to the RCTs and was at most moderate. Furthermore, we reported a higher incidence of patients with non-severe transaminase elevation. however, with only two patients with a reversible severe adverse event, this was not more than in RCTs.

From our observations, we conclude that kidney- and liver dysfunction should not be an absolute contraindication for the use of remdesivir in Covid-19 patients and that by regularly monitoring kidney- and liver function, treatment with remdesivir can be justified in these patients.

Conflict of interest statement

None to declare.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Figure legends

Figure 1. Changes in renal and liver function parameters after start of remdesivir treatment in patients with Covid-19. The data originates from the electronic health record of one hospital (Leiden University Medical Center, The Netherlands). In this figure changes in eGFR (figure 1A), AST (figure 1B) and ALT (figure 1C) laboratory measurements compared to baseline are shown. Baseline measurement was the most recent before start (max. 30 days), or if not available, the first measurement within 24 hours after the remdesivir prescription in the electronic health record. All colored data represent individual patient measurements. Patients in blue would have been excluded from clinical trials, based on their baseline measurements (eGFR: <50 ml/min/1.73m2, AST: >5 times upper limit of normal, AST: > 5 times upper limit of normal). In black the mean change per day is shown including a 95% confidence interval in grey.