

EARLY USE OF REMDESIVIR IN OBESE MALE PATIENTS WITH COVID-19 CAN IMPROVE THE PROGNOSIS

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Abstract

Early use of antivirals, including remdesivir, can be a useful solution in order to avoid severe progression of COVID-19 in patients with risk factors for unfavourable prognosis. Between December 2020 and January 2021, 98 males aged 18 years or older were admitted in our Infectious Diseases department (non-ICU); 47 of them were obese, with a BMI higher than 30 at admission. The study group included male obese patients who started remdesivir treatment during the first week after the symptoms' onset (early treatment); the control group included male obese patients who started remdesivir treatment more than seven days after symptoms' onset (later treatment). Only patients who received five days of remdesivir or more were included in the analysis. We analysed 9 patients with early administration of remdesivir and 27 patients with later treatment. The remdesivir administration was initiated in the first 36 hours after admission in almost all of the patients, in both groups. In the control group, 26/27 needed oxygen therapy (between 4 and 30 L/min) compared to 0/9 in the study group. In the study group, the patients developed only mild pneumonia and only 2 patients received dexamethasone. In conclusion, the remdesivir treatment might be of a greater benefit when initiated during the first five days of the disease, by preventing the evolution towards a severe form of disease and reducing the requirements of corticosteroids administration and oxygen supplementation.

Rezumat

Utilizarea medicației antivirale, inclusiv a remdesivirului din primele zile de boală, poate împiedica progresia COVID-19 către forme severe de boală, mai ales la pacienți cu factori de risc pentru un prognostic nefavorabil. În perioada decembrie 2020 – ianuarie 2021 într-o secție de Boli Infecțioase au fost internați în total 98 de pacienți de sex masculin, cu vârsta peste 18 ani; dintre aceștia, 47 erau obezi. Au fost incluși în studiu doar pacienții care au primit cel puțin cinci zile de remdesivir. În grupul de studiu au fost incluși pacienții la care tratamentul cu remdesivir s-a inițiat în primele 7 zile de la debutul simptomelor (tratament precoce); grupul de control a inclus 27 de pacienți cu tratament cu remdesivir inițiat la mai mult de 7 zile de la debutul bolii (tratament tardiv). Tuturor pacienților li s-a administrat remdesivir în primele 36 de ore de la internare. În grupul de studiu, 0 din 9 pacienți au necesitat oxigenoterapie, în comparație cu 26 din 27 de pacienți din grupul de control, care au avut nevoie de oxigenoterapie, între 4 și 30 litri oxigen/min. În grupul de studiu, pacienții au avut forme ușoare de pneumonie, doar 2 dintre aceștia au primit dexametazonă. În concluzie, tratamentul cu remdesivir poate avea un real beneficiu dacă este administrat în primele 5 zile de boală, prevenind evoluția către o formă severă de boală și reducând astfel necesitatea administrării corticosteroizilor și a oxigenoterapiei.

Keywords: remdesivir, COVID-19, risk factors, outcome, SARS-CoV-2

Introduction

COVID-19 has been challenging the healthcare systems all over the world. Around 20% of the patients developed hypoxemia, some of them even critical forms of the disease, with a rate of mortality around 50% [14, 15]. A good understanding of COVID-19 pathogenesis can lead to a better therapeutical strategy to improve outcomes [1, 13].

The first phase of COVID-19 is viral spreading, especially in the upper respiratory tract; if the disease ends by this stage, the prognosis is excellent [11]. The second phase is characterized by viral replication into the lungs, which leads to pneumonia and hypoxemia in some patients. The third phase is characterized

by the excessive immune response against SARS-CoV-2 and can conduct to acute respiratory distress syndrome (ARDS), multiple organ dysfunction and death [9].

Theoretically, antiviral therapy needs to be early administrated to limit the viral replication and to avoid severe lung injury. In the first phase and the early second phase of the disease, antivirals can play a more significant role in avoiding a worse outcome. Still, in the late second phase and the third phase, immunomodulatory therapy seems to be the most crucial therapeutics.

Some drugs have been proposed in COVID-19 as antiviral treatment, but the published data are inconclusive for their effectiveness [6]. An explanation is that most

of these studies have been conducted in patients with severe COVID-19 when viral replication is slowing down [4]. Instead, early use of antivirals can be a helpful solution to avoid COVID-19 progression to severe stages; the benefit could be more significant in patients with risk factors for unfavourable prognosis [7]. Remdesivir seems the most promising antiviral medication since the first months of the COVID-19 pandemic [1, 3].

Male sex, older age and obesity were identified as risk factors for worse disease [2, 5, 8]. Diabetes mellitus, cardiovascular, respiratory and chronic kidney diseases have also been proven to worsen the outcome in COVID-19 [2, 10]. These factors predicting unfavourable outcomes are essential for the early administration of antiviral treatment before the appearance of laboratory changes indicating COVID-19 severity.

Our study objective was to compare the outcome of COVID-19 male patients with obesity receiving remdesivir during the first week of the disease to that of the patients with later remdesivir administration. We have presumed that early antiviral therapy in these patients can have a more significant impact on the outcome than in other patients.

Materials and Methods

We performed a retrospective cohort study conducted in a COVID-19 dedicated hospital, “Prof. Dr. Matei Balș” National Institute of Infectious Diseases, Bucharest, Romania, in a non-ICU Department. Data were collected from patients' health records, and ethical approval was obtained from our Hospital Ethical Committee.

Study population

Between December 2020 and January 2021, 98 males aged 18 years or older were admitted to our department; 47 of them were obese, with a BMI higher than 30 at admission. Six of them did not receive remdesivir. Only patients who received five days of remdesivir or more were included in the analysis. The study group included patients who started remdesivir treatment during the first week after the symptoms' onset, and the control group included patients with later started remdesivir treatment. Nine patients were included in the study group. The patients' age in the study group ranged between 34- and 71-years-old. To match the two groups for age, five patients aged older than 71 years were not included in the control group. Finally, the study group included nine patients and the control group included 27 patients (Figure 1).

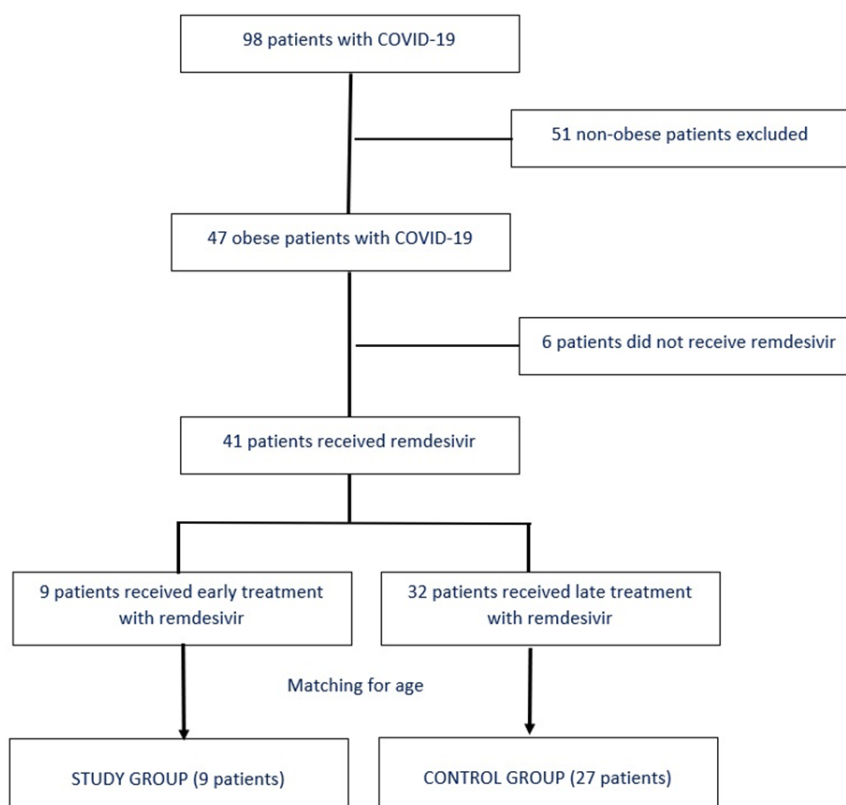


Figure 1.
Flowchart of patients' distribution

Treatment

Remdesivir was administrated following product approval, 200 mg by a single intravenous infusion in

the first day of treatment, and an intravenous infusion of 100 mg/day starting with the second day of treatment [17]. All patients received other medication as decided

by clinician, in accordance with hospital protocol – based on national guidelines, according to the phase of the disease: corticosteroids, anticoagulants, other immunosuppressive therapy (tocilizumab, anakinra), oxygen and supportive therapy.

Analysed data

The patients' data were analysed for the study group and the control group. The investigated parameters were: the presence of respiratory failure, the supplemental oxygen necessity (maximum volume/minute and duration of oxygen therapy), the severity of pneumonia and the risk of sequels, the need for immunosuppressive therapy and the length of stay.

Statistical analysis

Data were collected from patient records and were comparatively analysed between the two defined groups. The difference between means of continuous variables was assessed using the t-test/Mann Whitney-U test and the difference between proportions of categorical variables by using Fisher's exact test. Odds ratio (OR) and 95% confidence interval (CI) were calculated to

compare the need for oxygen therapy or the need for immunosuppressive treatment. The differences in outcomes between the study group and the control group were considered significant at $p < 0.05$ (two-sided). All statistical calculations were performed using MedCalc® Statistical Software version 19.8 (MedCalc Software Ltd, Ostend, Belgium).

Results and Discussion

We analysed nine patients with early administration of remdesivir and 27 patients with later administration of remdesivir. The baseline characteristics were similar for the two groups: the mean age, the mean BMI and the previous chronic diseases considered risk factors for severe COVID-19, except cardiovascular diseases, which were more frequent in the study group (Table I). The patients did not have any other risk factors for severe disease. The remdesivir administration was initiated in the first 24 - 36 hours after admission in almost all patients in both groups – Table I.

Table I

Characteristics of the patients in the study and the control group

Parameter	Study group	Control group	p value
Mean age	51.55	53.07	0.663
Mean BMI	36.06	35.51	0.778
Risk factors			
Diabetes mellitus	4/9	7/27	0.303
Cardiovascular diseases	8/9	12/27	0.022
Chronic pulmonary diseases	1/9	3/27	1
Dyslipidaemia	5/9	6/27	0.064
Corticosteroids before admission	0	3/27	0.303
Mean duration of the disease at admission (days)	3.11	9.81	< 0.0001
Mean duration until remdesivir administration after the symptoms' onset (days)	3.22	10.48	< 0.0001
Mean duration until remdesivir administration after admission (days)	1	1.48	0.303

$p < 0.05$ was statistically significant

The patients included in the study group started treatment with remdesivir in the first 5 days of the disease: one patient on the first day, one patient on the second day, 3 patients on the third day, 3 patients on the fourth day and one patient in the fifth day. Two patients were admitted in the first week of the disease in the control group, but they received remdesivir later after they developed hypoxemia. Other 25 patients from the control group were admitted in the second week of the disease; 21 received remdesivir since the first day of admission and two of them since the third day of admission.

The patients from the study group had normal levels of lymphocyte count, mild inflammatory syndrome and normal d-dimer levels. They performed two CT scans, one at admission and one after remdesivir cessation, and only mild ground-glass pneumonia was observed. None of the patients developed respiratory insufficiency, and only 2 patients received dexamethasone for five days, with a dosage of 8 mg/day.

The inflammatory syndrome was significantly higher in the control group, with a mean value of initial C reactive protein of 108.73 mg/L; in the study group, the mean value of initial C reactive protein was 12.59 mg/L. Only one patient from the study group had a high level of d-dimers at admission (higher than 200 ng/mL). In the control group, 19 patients had high levels of d-dimers (over 200 ng/mL) at admission, with a maximum value of 1267 ng/mL.

In the control group, the patients were admitted because of respiratory difficulties and 26/27 needed oxygen therapy – Table II. The need for oxygen treatment was significantly lower in the study group, 0/9 *versus* 26/27, OR = 0.055 (95% CI 0.003 - 0.986, $p = 0.049$). The mean volume of required oxygen was over 12 L/min (between 4 and 30 L/min) to maintain the oxygen saturation higher than 95%. The mean duration of oxygen therapy was almost 10 days (between 4 and 19 days) and was correlated with the severity of pneumonia.

Table II

Outcome measurements in the study and the control group

Parameter	Study group	Control group	p value
Hypoxemia and respiratory failure	0	26/27	< 0.0001
Hypoxemia	0	10/27	
Respiratory failure	0	16/27	
Mean oxygen volume/minute	NA	12.36 (between 4 and 30 litre/min)	
Oxygen therapy	0	26	< 0.0001
- Low flow (less than 15 L/min)	0	20	0.0001
- High flow (≥ 15 L/min)	0	6	0.1266
Mean duration of oxygen-therapy	NA	9.25 (between 0 and 19 days)	
Mean duration of admission	6.88	12.22	0.0001
Pneumonia on computed tomography	6	27	0.002
- Mild	6	0	
- Medium	0	12	
- Severe	0	15	
Secondary pulmonary fibrosis	0	15	0.0039
Need of cortisone	0	27	< 0.001
Need of non-corticosteroid immunosuppressive therapy	2	20	0.0064
- Tocilizumab		5	
- Anakinra		15	

p < 0.05 was statistically significant

All of the patients in the control group developed a medium or severe type of pneumonia, while the patients in the study group developed only a mild type of pneumonia – OR = 0.053 (95% CI 0.003 - 0.95, p = 0.046). All the patients from the control group received dexamethasone, 6 patients – 8 mg/day and 21 patients – 16 mg/day. In the control group, 74.1% of patients (20/27) were treated with immunomodulators other than corticosteroids, 15 patients received anakinra, and 5 patients received tocilizumab.

Fortunately, after administering immunosuppressive therapy with anakinra or tocilizumab, all the patients with severe respiratory failure had a good outcome with a slight decrease in the oxygen requirement. More than half of the patients from the control group (15 patients) were discharged with pulmonary changes on CT-scan and with low effort capacity. They will be re-evaluated in a pneumology department for specific kinesiotherapy.

At present, the use of remdesivir is recommended in hospitalized patients with severe COVID-19, requiring supplemental oxygen [5].

This study analysed the potential benefit of an early-stage administration of remdesivir in patients at high risk for severe COVID-19 – obese individuals of the male sex. Our findings revealed the superiority of initiating remdesivir treatment during the first five days of the disease, concerning the length of stay, additional oxygen requirement, patient outcome and potential sequelae. The patients receiving remdesivir earlier have not developed hypoxemia and respiratory failure and have not reached the point of corticosteroids indication. Furthermore, the patients in the study group only developed mild types of pneumonia, while those in the control group faced extensive pulmonary injury. Our approach represents a change of therapeutic strategy

because, in most studies published until now, remdesivir has been administrated later, in stages of moderate and severe COVID-19.

However, several studies support the idea that administrated earlier, even in severe cases, remdesivir was already related to better results. Avinash HR *et al.* [2] concluded that early administration of remdesivir (first 10 days of the disease) is related to a significantly lower mortality rate, 6.8% vs. 25%. Similarly, the ACTT-1 trial demonstrated that the administration of remdesivir during the first 10 days of the disease shows a significantly higher recovery rate than placebo and that starting remdesivir later during the condition appears to have a non-significant impact upon the outcome. Mehta *et al.* analysed 346 patients who received remdesivir treatment, and a mortality rate of 22% was reported, but the mortality rate was lower in earlier remdesivir treatment (2.8%) [8]. Finally, Wang *et al.* found a faster time for clinical improvement in patients receiving remdesivir within 10 days of symptoms' onset than placebo [14].

Our study had a limitation: it included only a small number of patients who received remdesivir in the first week of the disease, primarily because of the availability of remdesivir and due to later presentation of patients to the hospital in most of the cases.

Conclusions

Our findings suggest that the remdesivir treatment might be of a more significant benefit when initiated during the first five days of the disease by shortening the length of stay, preventing the evolution towards a severe form of illness and reducing the requirements of corticosteroids administration and oxygen supplementation.

Early use of Remdesivir in obese male patients with COVID-19 can improve the disease outcome, reducing the length of stay and the requirements of corticosteroids administration and oxygen supplementation.

Conflict of interest

The authors declare no conflict of interest.

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