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Effectiveness of dolutegravir in moderate severity COVID-19 patients: A single-center, randomized, double-blind, placebo-controlled trial

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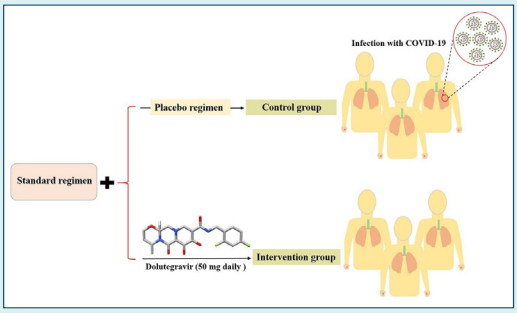
Abstract



Introduction: Drug repurposing as a low-cost, time-saving, and often less risky strategy has been attractive for the treatment of coronavirus disease 2019 (COVID-19) during the pandemic. This trial aimed to evaluate the effectiveness of dolutegravir, an HIV-1 integrase inhibitor, in admitted patients with moderate COVID-19.

Methods: This study was a randomized, double-blind, placebo-controlled clinical trial assessing the efficacy of dolutegravir in adults admitted to a hospital in Ghaemshahr, Mazandaran Province, Iran. Patients aged 18-80 years with early symptoms of moderate COVID-19, which was confirmed based on reverse transcription polymerase chain reaction (RT-PCR) and/or chest computed tomography (CT) scan, were considered to be included in this study. Patients were randomly assigned in a 1:1 ratio to receive 50 mg dolutegravir plus the standard treatment regimen or the same value of placebo plus the standard treatment regimen, daily for 7 days. The standard treatment regimen was remdesivir 200 mg on day 1 followed by 100 mg for five days or until discharge. The primary endpoint was recovery 10 days after the beginning of the study.

Results: Between August 22 and October 23, 2021, of 120 patients who were enrolled, 93 patients were randomly assigned to receive 50 mg dolutegravir (n = 46) or the placebo regimen (n = 47). No significant difference was observed between the two intervention groups based on the obtained results including frequency of respiratory modes during the first five days of admission, respiratory rate, and O_2 saturation during six time periods.

Conclusion: The results showed that in adult patients admitted to the hospital with moderate COVID-19, treatment with dolutegravir was not associated with improvement in clinical recovery. Larger randomized trials are required to provide more robust evidence about the effectiveness of dolutegravir.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2/2019-nCoV) is a novel 2019 betacoronavirus and its respiratory infection was first reported in Wuhan, China, in December 2019.[1-3] Coronavirus disease (COVID-19) has common symptoms such as fever, cough, and shortness of breath, leading to high morbidity and mortality rates, especially in the aging population.[4-7] According to the World Health Organization (WHO), on March 11, 2020, COVID-19 was declared a pandemic.[8,9] Early in the pandemic, scientists found that SARS-CoV-2, like SARS-CoV, attached to the angiotensin-converting enzyme 2 (ACE2) receptors in the human body through the receptor-binding domain (RBD) of its spike (S) proteins, but with a higher binding affinity (Fig. 1).[10-15]

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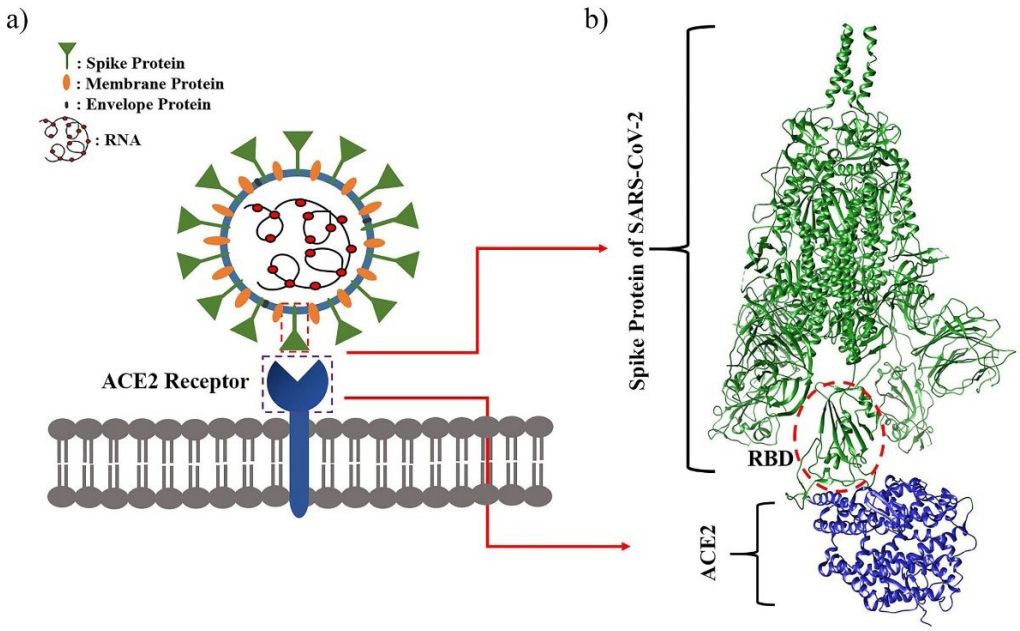

Fig. 1. Schematic representation of (a) SARS-CoV2 virus and (b) the cryo-electron microscopy data of its spike protein both in complex with human ACE2 receptor (PDB ID: 7VXM).[15]

Different parts of the virus, such as RNA-dependent RNA polymerase (RdRp), 3C-like protease (3CLpro, also known as main Protease, Mpro), papain-like protease (PLpro), and the S protein, could be potential targets for drug treatments.[16-21] Although the development of new and specific treatments to combat COVID-19 has been one of the most basic strategies, clinical studies could take years to evaluate.[4,22,23] Therefore, during the pandemic, the drug repositioning approach was considered an immediate strategy to reduce mortality and hospitalization,[24-28] an effective approach involving the identification of new therapeutic targets for existing de-risked drugs.[29,30] Compared with conventional drug discovery and development, this strategy could significantly reduce time, cost, and risk, as clinical effectiveness and safety data are often available.[31,32] To address this issue, many pharmaceutical agents have been repurposed for COVID-19 treatment, and thousands of clinical trials have been conducted to assess the safety and efficacy profile of the repurposed drugs. Drugs such as hydroxychloroquine, azithromycin, ritonavir/lopinavir, remdesivir, ivermectin, dexamethasone, and favipiravir were the most commonly prescribed medications among suggested repurposed drugs.[28,33,34] Based on findings from clinical studies, no or less effective repurposed agents have been identified so far. With the production of various types of vaccines and the vaccination of most people around the world, the COVID-19 pandemic has been controlled to a great extent.[35-37] But efforts to find effective treatment are still ongoing due to vaccine-escape mutants of COVID-19, anti-vaccination attitudes, and complications that some vaccines have shown.[38-43] Iran was also one of the Asian countries severely affected by the outbreak of Covid-19. Iran's Health Ministry announced the first confirmed case of COVID-19 in Qom on February 19, 2020, which unfortunately spread rapidly across the country.[44-46] According to the report of WHO, to date (12 April 2023), there have been 7,597,982 confirmed cases of infection with 145,571 deaths in Iran, https://covid19.who.int. Scientists in Iran have also tested several repurposed drugs in clinical studies.[47-49] Dolutegravir (DTG) is an integrase strand transfer inhibitor (INSTI) that has been approved for HIV-1 treatment in combination with other antiretroviral agents.[50-52] The proposed mechanism of action for dolutegravir involves the chelation of enzyme-bound cations, typically Mg^{2+} ions in the active site of the HIV-1 integrase. Thus, it prevents the integration of viral DNA into the host genome.[53,54] Dolutegravir displays excellent tolerability and minimal toxicity owing to its asymmetric effect on the host cells.[55,56] From the beginning of the pandemic until the time of writing this article, several computational studies have shown that dolutegravir could bind to important parts of SARS-CoV-2, such as RdRp residues and Mpro with high affinity.[57-62] It seems that if dolutegravir binding also occurs in vivo, the drug can fight COVID-19 in the body. To our knowledge, few clinical studies have assessed the impact of dolutegravir on COVID-19 treatment.[63] Taken together, in this study, the effectiveness of dolutegravir as an antiviral against moderate COVID-19 was evaluated. In this regard, a single-center, randomized, double-blind, placebo-controlled trial was conducted on adult patients admitted to Razi Hospital, Ghaemshahr, Iran.

Methods

Study design and participants

This study was a single-center, randomized, double-blind, placebo-controlled trial in that the effectiveness of dolutegravir along with the standard treatment regimen at the time of study in patients with moderate COVID-19 was evaluated. All patients were aged 18–80 years and were hospitalized at Razi Hospital, Ghaemshahr, Mazandaran Province. Patients with initial symptoms, including cough, weakness, lethargy, shortness of breath, and severe fatigue with or without fever (oral temperature > 37.8C), suspected of having COVID-19 were screened. COVID-19 infection in these patients was clinically confirmed using RT-PCR and/or chest CT scan results. Patients with arterial O_2 saturation ≥ 94, respiratory rate of < 24/min, and symptom onset ≤ 10 days before admission were included in the study. Patients with severe liver failure (Child-Pugh class C), history of COVID-19 or experimental drug use, any severe disability preventing cooperation, need for intubation on admission, allergy to dolutegravir, and those treated with phenytoin, fosphenytoin, oxcarbazepine, phenobarbital, primidone, and Stevens-Johnson syndrome were excluded. Patients who were pregnant or breastfeeding were excluded from the trial. All patients or their representatives provided written informed consent to participate in this study.

Randomization and masking

After registration, patients were randomly allocated to the two treatment arms dolutegravir and placebo in a 1:1 ratio. Block randomization was performed using sealed envelope online software, in which 93 patients were placed in 22 blocks of four and one block of five. To eliminate confounding by indication and severity, the trial was double-blind therefore patients and therapist clinicians were masked to patient allocation.

Procedures

After randomization, patients received the assigned drug. In the intervention group, dolutegravir plus the standard treatment regimen was administered at a dose of 50 mg daily for 7 days. Patients in the control group also received the placebo plus the standard treatment regimen for 7 days. The patients were assessed daily by skilled nurses from the first day to death or discharge. Information about each patient, side effects, and complications leading to drug discontinuation were recorded in report forms. Demographic, clinical, and radiological data and laboratory tests of the patients were recorded by the clinical pharmacy assistant in the data collection form.

Outcomes

The primary analysis was to evaluate the frequency of respiratory modes for both intervention arms during the first five days of admission, O_2 saturation, and respiratory rate during six time periods (admission time, days one to five). The secondary outcome of the trial was the number of patients who died, were discharged, or left the trial.

Statistical analysis

All analyses were performed using IBM SPSS statistical software, version 25. Results yielding a two-sided *P* value less than 0.05 were considered statistically significant. The Kolmogorov-Smirnov test was used to examine the data distribution. Continuous outcomes were expressed as mean ± standard deviation (SD) and median (interquartile range (IQR)) which were analyzed using the independent samples t-test or Mann-Whitney U test. Categorical data were described by frequency and percentage and were analyzed using Chi-squared tests.

Results

The first patient was screened on August 22, 2021, and random assignment ended on October 23, 2021. Of the 140 patients screened, 120 were eligible and were enrolled in the trial. Of these, 93 patients were randomly assigned to two intervention and control groups. 46 patients received 50 mg of dolutegravir and 47 patients received the placebo (Fig. 2).

The baseline characteristics of the enrolled patients, including demographic variables, diagnostic profiles, and vital signs on admission, are shown in Table 1.

Age and BMI were normally distributed among the demographic variables. The mean age of the patients in both groups was 49 years and the mean BMI was 28 kg/m². The median time from symptom onset to hospitalization was 7 days in both dolutegravir and placebo groups. Of the 46 patients, 24 (52.2 %) were men and 22 (47.8%) were female, whereas in the placebo group, 19 (40.4%) of the 47 patients were men and 28 (59.6%) female. Diabetes mellitus, hypertension (HTN), and ischemic heart disease (IHD) were the most common comorbidities observed in COVID-19 patients. As shown in Table 1, there were some random imbalances between the two groups, including more patients with IHD in the dolutegravir group than in the placebo group, 5 (10.9%) vs. 8 (17%), respectively ($P \geq 0.2$, chi-square test). Moreover, 10 (21.7%) patients in the dolutegravir group had diabetes, compared to 5 (10.6%) in the placebo recipients ($P = 0.169$, chi-square test). But, the number of HTN patients in both arms was almost equal, with 9 (19.6%) patients in the dolutegravir group and 8 (17%) patients in the placebo group ($P \geq 0.2$, chi-square test).

Primary outcomes

Respiratory mode

Table 2 shows the frequency of respiratory modes of the dolutegravir and control groups during the first five days of admission. There were no significant differences between the corresponding respiratory modes in the two treatment arms ($P \geq 0.2$).

O_2 saturation

A mixed between-within-subjects analysis of variance was conducted to assess the impact of two different interventions (dolutegravir, control) on patients' O_2 saturation across six time periods (admission time, days one to five) (Table 3).

There was no significant interaction between intervention type and time, Wilks' Lambda = 0.922, F (5, 80) = 1.363, P = 0.247, partial eta squared = 0.078. The main effect comparing the two types of intervention was not significant, F (5, 80) = .574, P = 0.720, partial eta squared = 0.035, suggesting no difference in the effectiveness of the two interventions. As shown in Fig. 3, the estimated marginal means of O_2 saturation during the six time periods in both intervention groups were calculated, which is not meaningful because it does not confirm previous results.

Respiratory rate

As shown in Table 4, a mixed between-within-subjects analysis of variance was conducted to assess the impact of two different interventions (dolutegravir, control) on patients' respiratory rate across six time periods (admission time, days 1 to 5).

Although there was a significant interaction between intervention type and time, [Wilks' Lambda = 0.640, F (5, 73) = 8.222, $P \leq 0.001$, partial eta squared = 0.360], the main effect comparing the two types of intervention was not significant, [F (5, 73) = 1.414, P = 0.229, partial eta squared = 0.088], suggesting no difference in the effectiveness of the two interventions. Such an outcome is also evident based on the estimated marginal means of the respiratory rate during six time periods between the two corresponding groups (Fig. 4).

Secondary outcomes

As mentioned earlier, in this study, there were 47 patients in the control group, all of whom recovered and were discharged, but in the dolutegravir group, one person died and one person left the trial ($P \geq 0.2$).

Discussion

In this randomized, placebo-controlled trial of patients hospitalized with moderate COVID-19 who received the standard treatment regimen, there was no observed benefit of intravenous dolutegravir in comparison with the placebo. Although vaccines have effectively controlled the pandemic and substantially reduced the severity of COVID-19, identifying different therapeutics that contain

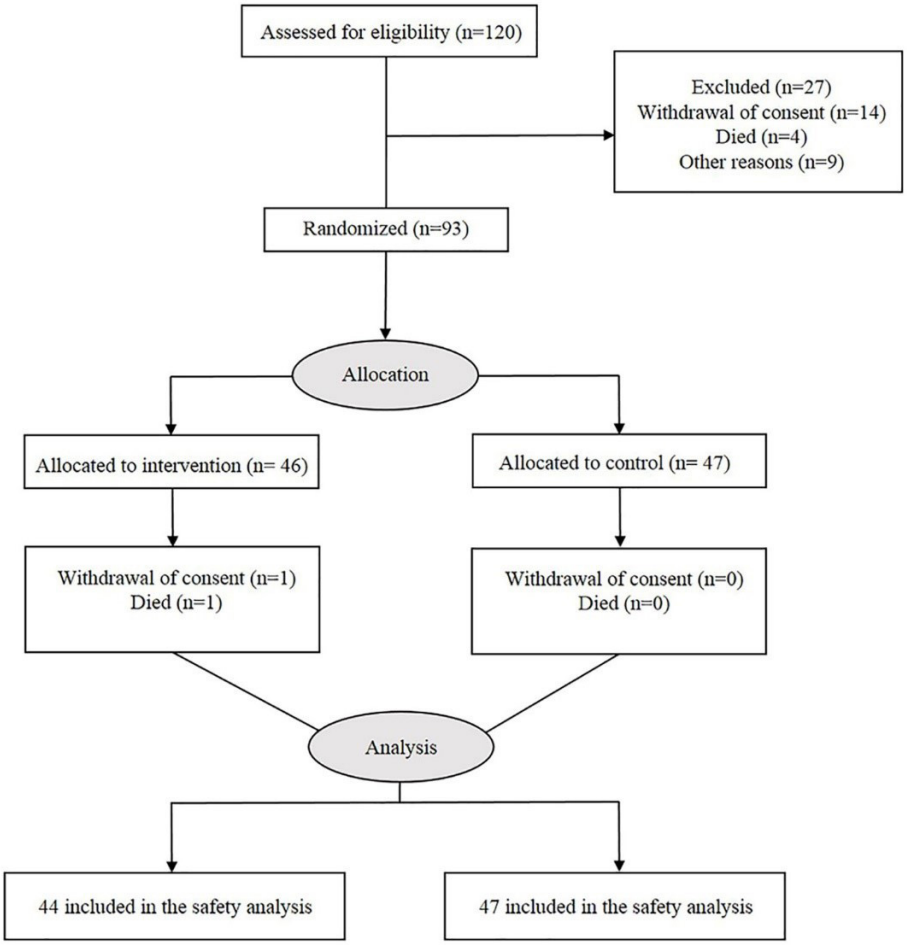

Fig. 2 The CONSORT flow diagram.

Table 1. Background characteristics (demographic, diagnostic, and vital signs on admission)

Variables			Dolutegravir group (n = 46) Median (IQR)	Control group (n = 47) Median (IQR)	*P* value[a]
Age (year), Mean (SD)			49.42 (13.78)	48.78 (14.73)	≥ 0.2[b]
BMI, Mean (SD)			27.52 (5.31)	28.49 (4.38)	0.066[b]
Symptom onset to hospitalization (day)			7 (2.25)	7 (3)	≥ 0.2
Gender, N (%)		Male	24 (52.2)	19 (40.4)	0.177[c]
		Female	22 (47.8)	28 (59.6)	
Concomitant diseases, N (%)		Diabetes M.	10 (21.7)	5 (10.6)	0.169[c]
		HTN	9 (19.6)	8 (17)	≥ 0.2[c]
		IHD	5 (10.9)	8 (17)	≥ 0.2[c]
		Asthma	0 (0)	1 (2.1)	≥ 0.2[c]
		COPD	2 (4.3)	0 (0)	≥ 0.2[c]
Vital signs		Temperature	37 (0.45)	37.1 (0.83)	≥ 0.2
		Respiratory rate	18 (2)	19 (2)	≥ 0.2
		Systolic BP	110 (22)	115 (30)	≥ 0.2
		Diastolic BP	70 (20)	70 (10)	≥ 0.2
Diagnostic profile, Mean (SD)	**Laboratory Data**	Hgb	12.89 (1.54)	12.36 (1.85)	≥ 0.2[b]
		Plt	182500 (101750)	170000 (70000)	≥ 0.2
		WBC	5200 (3175)	5400 (3200)	≥ 0.2
		PMNs	3250 (2350)	3000 (1900)	≥ 0.2
		Lymphocyte	900 (925)	1000 (500)	≥ 0.2
		BUN	25 (12.5)	21 (12.4)	0.055
		Cr	0.8 (0.3)	0.8 (0.3)	≥ 0.2
		Na	140 (4)	139 (3)	≥ 0.2
		K	4.2 (0.7)	4.1 (0.7)	0.113
		BS	118.5 (66)	126 (55)	≥ 0.2
		AST	35 (20.5)	33 (18)	≥ 0.2
		ALT	32 (25.25)	32 (22)	≥ 0.2
		AlkP	130.5 (55.75)	138 (59)	≥ 0.2
		ESR	42.5 (29.75)	30 (38)	≥ 0.2
		INR	1.1 (0.2)	1.1 (0.24)	≥ 0.2
		PH	7.4 (0.06)	7.4 (0.11)	≥ 0.2
		HCO3	33.55 (15.52)	30.4 (12)	0.073
		CRP^+, N (%)	35 (76.1)	42 (89.4)	0.094[c]
		PCR^+, N (%)	35 (76.1)	42 (89.4)	0.102[c]
	Radiological Findings	CT scan (%)	40 (10)	40 (20)	≥ 0.2

[a] Mann-Whitney U test; [b] Independent t-test, [c] Chi-square.

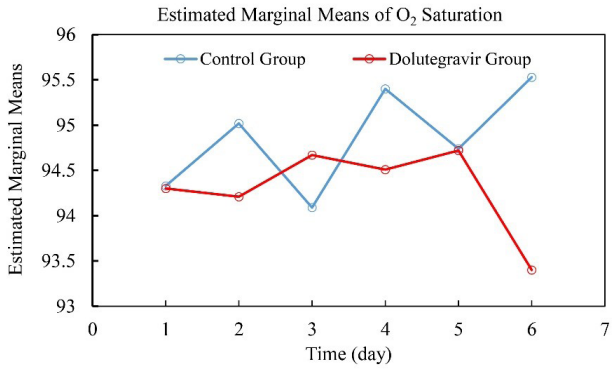

Fig. 3 Estimated marginal means of O_2 saturation during six time periods (admission time, days one to five) in the dolutegravir and placebo groups.

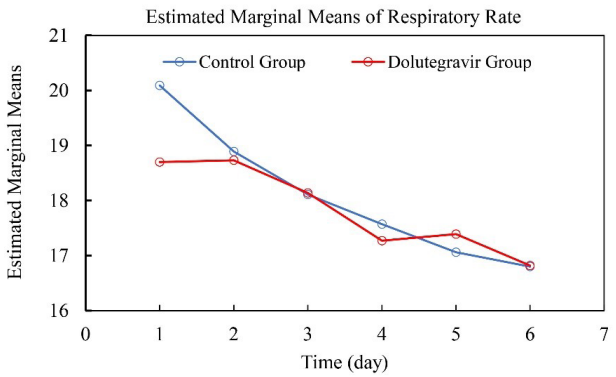

Fig. 4 Estimated marginal means of respiratory rate during six time periods (admission time, days one to five) in the dolutegravir and placebo groups

Table 2 The frequency of respiratory modes between two groups during the first five days of admission

Day	Respiratory mode	Dolutegravir group No. (%)	Control group No. (%)	*P* value*
1	Room air	28 (60.86)	25 (53.20)	≥ 0.2
	Nasal O_2	12 (26.08)	13 (27.65)	
	Room - Nasal	6 (13.04)	9 (19.15)	
2	Room air	25 (54.34)	27 (57.45)	≥ 0.2
	Nasal O_2	13 (28.26)	11 (23.40)	
	Room - Nasal	8 (17.40)	9 (19.15)	
3	Room air	29 (63.05)	29 (61.70)	≥ 0.2
	Nasal O_2	10 (21.73)	11 (23.40)	
	Room - Nasal	7 (15.22)	7 (14.90)	
4	Room air	33 (71.73)	30 (63.83)	≥ 0.2
	Nasal O_2	8 (17.39)	11 (23.40)	
	Room - Nasal	5 (10.88)	6 (12.77)	
5	Room air	32 (69.57)	32 (68.08)	≥ 0.2
	Nasal O_2	8 (17.39)	8 (17.02)	
	Room - Nasal	6 (13.04)	7 (14.90)	

*Chi-square test.

Table 3. O_2 saturation during six time periods (admission time, days 1 to 5) in the dolutegravir and placebo group

	Group	Mean	Std. Deviation
O_2 saturation on admission	Control	94.33	3.992
	Dolutegravir	94.30	3.949
O_2 saturation (Day 1)	Control	95.02	2.899
	Dolutegravir	94.21	3.649
O_2 saturation (Day 2)	Control	94.09	3.544
	Dolutegravir	94.67	3.956
O_2 saturation (Day 3)	Control	95.40	2.953
	Dolutegravir	94.51	3.990
O_2 saturation (Day 4)	Control	94.74	3.600
	Dolutegravir	94.72	4.361
O_2 saturation (Day 5)	Control	95.53	2.798
	Dolutegravir	93.40	13.798

Table 4. Respiratory rate during six time periods (admission time, days 1 to 5) in the dolutegravir and placebo group

	Group	Mean	Std. Deviation
Respiratory rate on admission	Control	20.09	3.673
	Dolutegravir	18.70	1.286
Respiratory rate (Day 1)	Control	18.89	3.160
	Dolutegravir	18.73	1.809
Respiratory rate (Day 2)	Control	18.11	2.166
	Dolutegravir	18.14	2.007
Respiratory rate (Day 3)	Control	17.57	2.429
	Dolutegravir	17.27	2.095
Respiratory rate (Day 4)	Control	17.06	2.543
	Dolutegravir	17.39	2.626
Respiratory rate (Day 5)	Control	16.80	2.286
	Dolutegravir	16.82	3.322

safe and effective drugs is still important. Remdesivir, favipiravir, hydroxychloroquine, ribavirin, interferon, and intravenous immunoglobulin (IVIG) were among the drugs that received much attention for treatment.[28,33,34,63,64] Unfortunately, no effective therapeutic approach has been achieved so far. Dolutegravir is the first second-generation INSTI with FDA approval and has recently been used to treat HIV-1 infection.[50-52] As mentioned earlier, in silico results showed that dolutegravir can efficiently bind to the SARS-CoV-2 Mpro and RdRp active sites,[57-62] however, few clinical trials have been conducted so far. In our study, the primary outcome analysis reflected the ineffectiveness of dolutegravir intervention in improving patients. No significant difference was observed in the respiratory modes of the dolutegravir group compared with the placebo during the first five days of admission. Monitoring the O_2 saturation level and respiratory rate of patients also showed that dolutegravir did not have a significant effect on moderate COVID-19 treatment. The slight differences in mortality and withdrawal rates between the dolutegravir and placebo groups were also not significant. To the best of our knowledge, only one trial has been conducted to test the efficacy of dolutegravir against COVID-19.[63] In this trial, which was performed in Iran, the effectiveness of atazanavir/ritonavir/dolutegravir (300/100/500 mg once a day) plus hydroxychloroquine with lopinavir/ritonavir (400/100 mg twice a day) plus hydroxychloroquine was compared. Both groups received hydroxychloroquine 400 mg BD on the first day and then 200 mg BD on the following days. 62 patients with moderate or severe symptoms of COVID-19 who entered the study were randomly assigned to two treatment groups and received the designated medications for 10 days. Their results showed that the atazanavir/ritonavir/dolutegravir treatment regimen has considerable advantages in reducing the severe course of COVID-19 when compared to the lopinavir/ritonavir regimen.[63] In general, the accurate interpretation of results is affected by limitations that should not be ignored. A control group was not used in this study, so the efficacy of the corresponding treatment groups was not compared with standard care during the study. The trial was not blinded and the study population size was small. Another point is that the exact efficacy of dolutegravir was not determined in this trial, since the therapeutic effect of dolutegravir in combination with atazanavir has been evaluated. However, our study also has limitations that should be considered. The number of diabetic patients was higher in the dolutegravir group and patients with IHD in the placebo were more than in the other group. The number of males and females in the dolutegravir group was almost

equal, while the number of males in the placebo group was significantly less than females. In addition, the female and male patients were not equally distributed between the two groups. On the other hand, due to the small number of participants in this trial, the results should be interpreted with caution and confirmed through larger randomized controlled trials.

Conclusion

In summary, according to our findings, dolutegravir cannot improve the clinical symptoms in adult patients with moderate COVID-19 and it seems that it does not have much effect on the treatment process. However, further studies with larger populations are highly recommended for more accurate assessment.

Acknowledgments

The Authors would like to thank Mazandaran University of Medical Sciences and the Infectious Diseases Department of Razi Hospital in Ghaemshahr City for their cooperation.

Competing Interests

The authors declare that there is no conflict of interest.

Ethical Statement

The study protocol was approved by the Mazandaran University of Medical Sciences (IR.MAZUMS.REC.1399.972) and registered in the Iranian Registry of Clinical Trials (IRCT), number IRCT20200328046886N3, which is available at https://www.irct.ir/trial/55549.

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Research Highlights

What is the current knowledge?

√ Since the start of the COVID-19 pandemic in January 2020, many trials have been conducted to find an effective treatment. Although today, due to worldwide vaccination, the pandemic has been controlled to a considerable extent, still a completely effective drug treatment for COVID-19 has not been found.

What is new here?

√ This study was the first randomized, double-blind, placebo-controlled clinical trial, to our knowledge, of intravenous dolutegravir added to remdesivir as the standard treatment regimen in adult patients with moderate COVID-19. This trial showed that treatment with dolutegravir was not associated with improvement in clinical recovery.

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