Outcomes of high-risk adult outpatients with haematological malignancies treated with early remdesivir therapy during the SARS-CoV-2 omicron era: experiences from the national centre of Hungary

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Short Report

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Abstract

Objectives

Emerging evidence suggests that remdesivir might improve clinical outcome of high-risk outpatients with COVID-19. Our aim was to evaluate characteristics and outcomes of non-hospitalized adults with haematological malignancies diagnosed with COVID-19 and treated with early remdesivir therapy during the omicron wave.

Methods

A single-centre prospective cohort study was performed among adult patients between February–June 2022, during the circulation of PANGO subvariants BA.2, BA.4 and BA.5 in Hungary. Patients were enrolled based on *pre-defined* criteria. Clinical characteristics (demography, comorbidities, vaccination status, imaging, treatment, and disease course) and outcomes (COVID-19 related hospitalisation, oxygen supplementation, intensive care support, *all-cause* death) were assessed at 28-days post-treatment.

Results

Altogether 127 patients were enrolled: 51.2% (65/127) were female with a median age of 59 ± 22 (21—92) years, and 48.8% (62/127) had active haematological malignancy. At 28-days post-treatment, 7.1% (9/127) of patients required COVID-19 related hospitalisation, 2,4% (3/127) required oxygen supplementation, 1,6% (2/127) required intensive care, and 0.8% (1/127) died due to a non-COVID-19 related secondary infection at the intensive care unit, all with haematological malignancies.

Conclusion

Early remdesivir treatment might be a feasible strategy among high-risk outpatients with haematological malignancies and COVID-19 during the omicron wave.

Introduction

Management strategies of patients infected with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) depend on the clinical context, patient-level risk factors and treatment availability [1]. Outpatients who are unvaccinated or partially immunized, as well as elderly, obese or immunocompromised are at higher risk for severe or progressive disease [2]. Therefore, early initiation of therapy might be warranted in these subpopulations [2].

Antiviral ttreatment options include monoclonal antibodies, and direct antiviral agents [1]. Monoclonal antibodies targeting spike protein of the SARS-CoV-2 have been shown to provide clinical benefit among

certain clinical circumstances in treating Corona Virus Disease 2019 (COVID-19) [1]. However, the anticipated in vivo activity of different monoclonal antibodies greatly varies depending on the viral subvariant type, therefore limiting universal applicability [1]. Currently, recommended antiviral drugs against SARS-CoV-2 are polymerase inhibitors remdesivir and molnupiravir, and the protease inhibitor combination nirmatrelvir/ritonavir [1]. Remdesivir has already been licenced for in-hospital treatment of SARS-CoV-2 infected patients but recent data support its use in early COVID-19 in the outpatient setting, by lowering the overall risk of hospitalisation and disease progression [3, 4].

Access to the different monoclonal antibodies and direct antiviral agents varies by country. In Hungary, particularly in the context of lacking oral antivirals during our study period, remdesivir became the single therapeutic option for high-risk outpatients. The aim of the present study was to evaluate clinical characteristics and outcomes of high-risk adult outpatients with haematological malignancies receiving early remdesivir treatment in the outpatient setting, during the *Phylogenetic Assignment of Named Global Outbreak* (PANGO) BA.2, BA.4 and BA.5 omicron subvariant predominance in Hungary [5].

Materials And Methods

Study design and setting

A single-centre prospective cohort study was conducted among SARS-CoV-2 infected patients who were at high risk for disease progression and received early remdesivir therapy between February–June 2022. Our centre is a national-level referral institution of COVID-19, with a high-influx COVID-19 Outpatient Department during the pandemic (*Supplementary file 1.).* The study design was in accordance with the Helsinki Declaration and national ethical standards. The study protocol was approved by the Institutional Review Board of South Pest Central Hospital, National Institute of Haematology and Infectious Diseases (IKEB-14/2020). Written informed consent was obtained from each included patient.

Patient eligibility and inclusion

All adult patients (≥ 18 years at diagnosis) with confirmed SARS-CoV-2 nasopharyngeal sample positivity by real-time polymerase chain reaction (RT-PCR), and ≥ 1 pre-defined risk factor for disease progression were eligible for inclusion. Patients were included consecutively at COVID-19 diagnosis, if they consented to receive remdesivir for a minimum of 3 days, promptly started after diagnosis ascertainment. COVID-19 severity was given according to the *World Health Organization* (WHO) criteria [8]. Pre-defined patient-level risk factors were essential hypertension, obesity (body mass index > 25 kg/m^2), chronic cardiovascular disease, chronic cerebrovascular disease, chronic pulmonary disease, chronic renal disease, chronic liver disease, diabetes mellitus, immunocompromised states, and active onco-haematological malignancy.

Data collection

Patient data were collected anonymously through electronic medical records and clinical charts and were recorded in a structural database. Data collected were: 1) age, gender at birth, 2) comorbidities, 3) COVID-

19 vaccination status, previous SARS-CoV-2 infections, 4) disease course (onset of typical symptoms, disease severity), 5) nasopharyngeal and blood SARS-CoV-2 RT-PCR results, 6) results of chest computed tomography (CT) scans, 7) details of remdesivir treatment, 8) clinical outcomes. Baseline variables were recorded at COVID-19 diagnosis.

Therapeutic strategies

Included patients received 200 mg remdesivir *quaque die* (QD) intravenously on the day of diagnosis, diluted in 0.9% saline according to instructions of the manufacturer, and 100 mg remdesivir QD on the following days. The protocol suggested 3 days of standard treatment, but at the discretion of the attending physician, prolongation of treatment was permitted for a total of 5 days.

Outcomes and patient follow-up

The primary endpoint was the need for hospitalization due to COVID-19. Secondary endpoints were *all-cause* death, need for oxygen supplementation and need for intensive care unit admission. All outcome measures were assessed at + 28 days after the end of remdesivir treatment. Patient follow-up is detailed in *Supplementary file 1.*

Statistical analysis

Continuous variables are reported by median ± interquartile range (IQR), with minimum–maximum ranges. The Shapiro-Wilk test was used for normality check. Categorical variables are reported as absolute numbers (n) with relative percentages (%). A subgrouping for comparison of haematological and non-haematological patients was *a priori* planned. *Chi*-squared and *t*-tests were used for statistical comparison. Statistical significance was decided at a two-sided *p*-value of < 0.05.

Results

In total, 127 patients were enrolled during the study period (Table 1.). Among these, 48.8% (n = 62) had an active haematological malignancy. These were non-Hodgkin lymphoma (n = 25; 40.3%), acute leukaemia (n = 16; 25.8%), chronic lymphocytic leukaemia (n = 10; 16.1%), myeloproliferative neoplasms (n = 4; 6.5%), Hodgkin's lymphoma (n = 4; 6.5%) and myelodysplastic syndrome (n = 3; 4,8%). Median age at diagnosis was 59 ± 22 (21–92) years, 51.2% (n = 65) of included patients were female in the cohort. Gender, age and comorbidities were equally distributed in the groups, except for essential hypertension, active oncological and systematic autoimmune diseases, which were statistically more frequent in the non-haematological subgroup. Presence of SARS-CoV-2 RNAemia was found at similar rates between subgroups. Upon chest CT examinations, eighteen patients (17.6%) had alterations typical for COVID-19. More patients were fully vaccinated in the non-haematological subgroup, but severity of symptoms was balanced. The median time from symptom onset to first dose of remdesivir was 3 ± 3 (0–63) days, with no statistically significant difference between groups. Nine patients (7.1%) had to be admitted to the hospital, three (2.4%) required oxygen supplementation, two patients (1.6%) were transferred to intensive care unit and one patient (0.8%) died within the study period. All negative outcomes occurred in the

haematological subgroup. The 3-day therapy protocol was more frequently administered among non-haematological patients (38.6% vs. 12.9%, $p < 0.01$).

Table 1
Baseline characteristics and outcomes of patients included in the study.

PARAMETER	Total (n = 127)	Haematological patients (n = 62)	Non-haematological patients (n = 65)	*p*-value
Age (years, median ± IQR; min – max)	59 ± 22; 21–92	57 ± 24; 21–82	63 ± 21; 31–92	0.24
Male (n, %)	62; 48.8%	32; 51.6%	30; 46.2%	0.54
Comorbidities (n, %):				
Essential hypertension	55; 43.3%	15; 24.2%	40; 61.5%	< 0.01
Chronic cardiovascular disease	9; 7.1%	2; 3.2%	7; 10.8%	0.10
Chronic pulmonary disease	12; 9.4%	3; 4.8%	9; 13.8%	0.08
Chronic renal disease	3; 2.4%	1; 1.6%	2; 3.1%	0.59
Chronic liver disease	3; 2.4%	0; 0%	3; 4.6%	0.09
Chronic cerebrovascular disease	1; 0.79%	0; 0%	1; 1.5%	0.33
Diabetes mellitus	25; 19.7%	9; 14.5%	16; 24.6%	0.15
Active oncological malignancy	20; 15.7%	3; 4.8%	17; 26.1%	< 0.01
Active haematological malignancy	62; 48.8%	62; 100%	0; 0%	n.a.
Systematic autoimmune disease	17; 13.4%	4; 6.5%	13; 20.0%	< 0.01
Chronic systemic corticosteroid treatment	4; 3.2%	2; 3.2%	2; 3.1%	0.96
Chronic immunosuppressive drug use	14; 11.0%	6; 9.7%	8; 12.3%	0.64
Chronic alcohol use	1; 0.79%	0; 0%	1; 1.5%	0.33
Chronic tobacco use	6; 4.7%	1; 1.6%	5; 7.7%	0.11
Obesity	32; 25.2%	11; 17.7%	21; 32.3%	0.06

n.a.: not applicable.

* In proportion to the number of tested patients.

PARAMETER	Total (n = 127)	Haematological patients (n = 62)	Non-haematological patients (n = 65)	*p*-value
COVID-19 vaccination status (n, %):				
Full immunization (≥ 3 doses)	87; 68.5%	34; 54.8%	53; 81.5%	< 0.01
Partial immunization (< 3 doses)	30; 23.6%	21; 33.9%	9; 13.8%	0.01
No data (n, %)	10; 7.9%	7; 11.3%	3; 4.6%	0.16
Previously documented SARS-CoV-2 infection (n, %):				
Within 3 months	2; 1.6%	2; 3.2%	0; 0%	0.14
Over 3 months	8; 6.3%	6; 9.7%	2; 3.1%	0.13
No previous infection	49; 38.6%	24; 38.7%	25; 38.5%	0.98
No data	68; 53.5%	30; 48.4%	38; 58.5%	0.26
COVID-19 severity (n, %):				
Asymptomatic	44; 34.6%	19; 30.6%	25; 38.5%	0.35
Non-severe	82; 64.6%	42; 67.7%	40; 64.5%	0.47
Severe	1; 0.8%	1; 1.6%	0; 0%	0.30
SARS-CoV-2 RNAemia positivity* (n, %)	30/117; 25.6%	16/56; 28.6%	14/61; 23.0%	0.43
Lung infiltration typical for COVID-19 on chest CT scan* (n, %)	18/102; 17.6%	9/55; 16.4%	9/47; 19.1%	0.52
Time from symptom onset to remdesivir (days, median ± IQR, min–max)	3 ± 3; 0–63	4 ± 5; 0–63	3 ± 2; 0–14	0.13
Time from first positive respiratory SARS-CoV-2 PCR to remdesivir (days, median ± IQR, min–max)	0 ± 1; 0–26	0 ± 1; 0–26	0 ± 1; 0–4	0.35

n.a.: not applicable.

* In proportion to the number of tested patients.

PARAMETER	Total (n = 127)	Haematological patients (n = 62)	Non-haematological patients (n = 65)	*p*-value
Time from first positive to first negative respiratory SARS-CoV-2 PCR (days, median ± IQR, min−max)	22 ± 19; 0–78	27 ± 16; 5–78	15 ± 8; 0–45	0.20
Clinical outcomes (n, %)				
Need for hospitalization due to COVID-19	9; 7.1%	9; 14.5%	0; 0%	< 0.01
Need for oxygen supplementation	3; 2.4%	3; 4.8%	0; 0%	0.07
Need for intensive care unit admission	2; 1.6%	2; 3.2%	0; 0%	0.14
All-cause death	1; 0.79%	1; 1.6%	0; 0%	0.30
Administered doses of remdesivir (n, %)				
Standard course (3 days)	49; 38.6%	8; 12.9%	41; 63.1%	< 0.01
Prolonged course (5 days)	78; 61.4%	54; 87.1%	24; 36.9%	< 0.01
n.a.: not applicable.				
* In proportion to the number of tested patients.				

Discussion

Present study

This single-centre prospective cohort study evaluated clinical characteristics and outcomes of high-risk adult outpatients with haematological malignancies receiving early remdesivir therapy in the SARS-CoV-2 omicron variant era. We documented low rates of hospitalization and *all-cause* death, while all negative outcomes occurring among patients with malignant haematological diseases.

Current literature

In the literature, multiple studies have assessed the therapeutic effect of an early 3-day remdesivir therapy [2, 4]. A randomized, double-blind, placebo-controlled study involving 562 non-hospitalized high-risk patients documented an 87% survival among patients receiving the 3-day remdesivir therapy, compared to the placebo arm [2]. Also, a matched-pair retrospective study comparing COVID-19 related hospitalisation and acute respiratory failure among outpatients treated with a 3-day remdesivir to

placebo reported a 75% lower rate of hospital admission, and a 95% lower rate of acute respiratory failure among patients receiving remdesivir [4].

Clinical data of SARS-COV-2 infected patients with active haematological malignancies shows a higher risk for progression to severe disease [7]. In an Italian study, type of malignancy (active lymphoblastic leukaemia), disease activity and recently administered chemotherapy increased the odds of severe clinical course or death [7]. Different comprehensive strategies, such as remdesivir plus monoclonal antibodies or remdesivir plus convalescent plasma therapy proved to be successful for protection among patients with an active haematological malignancy [8]. However, efficacy of monoclonal antibodies depends on the circulating variant, whereas accessibility of convalescent plasma therapy may be hindered in some low-income settings [1].

During the alfa and delta waves, monoclonal antibody therapies were generally available for the treatment of SARS-CoV-2 infected high-risk outpatients [1]. In addition, in Hungary, favipiravir had been included in the national COVID-19 guideline based on an *off-label* approval by the National Institute of Pharmacy and Nutrition. Subsequent trials, however, did not confirm its positive effect on clinical outcomes in the early phase of COVID-19 [9, 10].

So far, two orally administered antivirals became available in some European countries with full or conditional approval by the *European Medicine Agency*. The cysteine protease inhibitor nirmatrelvir/ritonavir and the replication inhibiting molnupiravir proved to be effective not only in *in vitro* studies, but also in real-life settings during the PANGO BA.2 dominance [1, 6]. These drugs are easy to administer and possess good bioavailability with generally acceptable side-effect profiles [1, 6]. However, in countries with limited accessibility to oral antivirals against SARS-CoV-2, administration of remdesivir may be retained as an essential treatment strategy for COVID-19. Furthermore, among patients with haematological malignancies, where viral persistence, longer viral shedding and viremia is a problematic tendency, a parenterally administered medication could be a rational option [8]. This might be mirrored by the change in WHO recommendations where indication for remdesivir was expanded to the outpatient setting, while also acknowledging its efficacy against SARS-CoV-2 PANGO variants BA.2, BA.4, and BA.5 [2, 6].

Study limitations

The present study has some limitations. First, we did not identify SARS-CoV-2 variants of each patient. We considered the omicron variant of SARS-CoV-2 as dominant in Hungary based on surveillance samples to the *European Centre for Disease Control and Prevention* by national authorities [5]. Second, a relatively small number of patients were involved in the study. Third, as the study design is a simple observational study, no randomization or placebo-control was feasible at the outpatient setting for high-risk patients.

Conclusion

In this single-centre prospective cohort study conducted during the SARS-CoV-2 omicron wave, outcomes of high-risk adult outpatients with haematological malignancies treated with early remdesivir therapy were favourable, providing a clinically feasible strategy against COVID-19.

Abbreviations

COVID-19
Coronavirus Disease 2019
CT
computed tomography
IQR
interquartile range
PANGO
Phylogenetic Assignment of Named Global Outbreak
PCR
polymerase chain reaction
QD
once daily [*quaque die*]
RT-PCR
real-time polymerase chain reaction
SARS-CoV-2
severe acute respiratory syndrome coronavirus 2
WHO
World Health Organization

Declarations

Authors' contribution: ZsG: data collection, data analysis, preparation of study protocol, preparation of the manuscript; BGSz: management of patients, data analysis, preparation of study protocol, preparation of the manuscript; AÁ: management of patients, review of the manuscript; ZsV: management of patients, review of the manuscript; NKD: management of patients, review of the manuscript; JSz: management of patients, review of the manuscript; JS: management of patients, review of the manuscript; VNI: preparation of study protocol, review of the manuscript; BL: management of patients, preparation of study protocol, data analysis, preparation and review of the manuscript. Authors participated equally in patient management and manuscript revision. All authors have read and approved the final manuscript for publication.

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Consent to participate: Written informed consent was obtained from each patient.

Data, Material and/or Code availability: Anonymised data of patients are available from the corresponding author on reasonable request.

Ethics Approval: The study was in accordance with the Helsinki Declaration and national ethical standards. The institutional review board of South Pest Central Hospital, National Institute of Haematology and Infectious Diseases approved the study protocol. The National Institute of Pharmacy and Nutrition approved the *off-label* use of remdesivir detailed in the manuscript (*https://www.ema.europa.eu/en/documents/product-information/veklury-epar-product-information_hu.pdf*).

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Supplementary Files

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