Official journal of the Spanish Society of Chemotherapy

Letter to the Editor

Revista Española de Quimioterapia
doi:10.37201/req/069.2023

Ana Segura Fábrega[1]
Ignacio Pérez Catalán[1]
Iris Gómez Alfaro[2]
Sergio García Muñoz[3]
Celia Roig Martí[1]
Noelia Rodríguez Lozano[2]
Sofía Folgado Escudero[1]
María Varea Villanueva[1]
Adriana Gascón Buj[4]
Miguel Torres García[5]
Roberto Reig Valero[6]
Raúl Ferrando Piqueres[3]
Jorge Usó Blasco[1]

Association of nirmatrelvir/ritonavir and remdesivir as treatment for SARS-CoV-2 infection in immunocompromised patients with hematologic malignancies. Series of four cases

[1]Internal Medicine, General University Hospital of Castellón, Castellón de la Plana, Spain
[2]Clinical Microbiology, General University Hospital of Castellón, Castellón de la Plana, Spain
[3]Hospital Pharmacy, General University Hospital of Castellón, Castellón de la Plana, Spain
[4]Hematology, General University Hospital of Castellón, Castellón de la Plana, Spain
[5]Pneumology, General University Hospital of Castellón, Castellón de la Plana, Spain
[6]Intensive Care Medicine, General University Hospital of Castellón, Castellón de la Plana, Spain

Article history
Received: 28 May 2023; Revision Requested: 26 June 2023; Revision Received: 29 June 2023;
Accepted: 11 July 2023; Published: 3 October 2023

Sir,

The choice of treatment against SARS-CoV-2 infection in patients with hematologic malignancy with active drug therapy is challenging, given the absence of randomized studies in this patient profile. In addition, the behavior of the virus in this group is different, with evidence of sustained viral replication over time [1]. In this regard, there have been reports of viral persistence and even recurrent pneumonia, especially in patients with hematological malignancies who have received treatment with anti-CD20 drugs in the 6 months prior to infection [2]. In addition, systemic corticosteroids could favor recurrence by decreasing viral clearance [3].

For its treatment, antivirals such as nirmatrelvir/ritonavir or remdesivir have been used in monotherapy, even in extended regimens, with different results [4,5]. Good results have also been reported in vitro and in vivo, in this subgroup of patients, with the combination of antivirals (nirmatrelvir/ritonavir and remdesivir) and even monoclonal antibodies [6-8].

In this context, and following a decision by a multidisciplinary committee for therapy against SARS-CoV-2, it was agreed to select those patients with hematological neoplasia under active treatment who could benefit from antiviral bitherapy, given the clinical suspicion of viral persistence and failure of previous antiviral monotherapy. The experience is described below.

Four patients (median age 65 years, interquartile range [IQR] 58-73) with oncohematologic disease on active treatment required admission for Covid-19 during 2022 (Table 1); two of them had pneumonia. In all of them, rituximab was part of the therapeutic regimen. The complete vaccination regimen had been administered in all patients, with the development of IgG anti-S antibodies against SARS-CoV2 in one of the cases (this was not analyzed in the remaining patients). Definitive antiviral treatment with concurrent antiviral bitherapy (nirmatrelvir/ritonavir and remdesivir) for 5 days was administered after having received, in all four cases, one or two full 5-day regimens of nirmatrelvir/ritonavir. The timing of administration was late in all cases, with a median of 48.5 days of symptoms ([IQR] 19.5-117). Although three of them did not have respiratory failure at the time of treatment, it is noteworthy that patient 3 had previously been admitted to the intensive care unit (ICU) for severe respiratory failure. Regarding the SARS-CoV-2 variant, in two patients it was confirmed by sequencing that the variant at the onset of symptoms and the variant prior to the start of antiviral bitherapy were the same, confirming the persistence of the infection despite prior antiviral monotherapy. In patient 1 it could not be confirmed since only the variant at symptom onset (Ómicron BQ.1.1.; variant derived from BA.5) was sequenced and prior to the start of bitherapy a rapid test (VIASURE SARS-CoV-2 Varian III Real Time PCR Detection Kit) was performed which confirmed the presence of the Q954H gene and not of A2710T, a finding common to Ómicron BA.2, BA.4 and BA.5.

Only one patient required ICU admission after bitherapy: he was admitted with pneumonia and severe respiratory failure and required non-invasive mechanical ventilation. After a slight improvement, he was transferred to the conventional hospital ward, at which time antiviral bitherapy was administered in view of the slow improvement and persistence of positive CRP with low Kt. Finally, he presented a new respiratory worsening and died. The remaining 3 patients responded effectively to the administration of this treatment, and only one of them died after 4 months due to progression of his hematologic disease. They also did not require new admission due to recurrence of the infection, nor new antiviral treatment, and

Correspondence:
Ignacio Pérez Catalán
Internal Medicine, General University Hospital of Castellón, Castellón de la Plana, Spain
E-mail: nachocs13@gmail.com

Table 1 **Clinical cases that have received remdesivir and nirmatrelvir/ritonavir as antiviral bi-therapy.**

	CASE			
CLINICAL CONTEXT	1	2	3	4
Age (years)	55	69	77	61
Sex	Female	Male	Male	Male
Hematological malignancy (treatment line)	DLBCL (third line, CART therapy approved)	Mantle cell lymphoma (fourth line)	DLBCL (first line)	Mantle cell lymphoma (fourth line)
Treatment (time from last dose to onset of symptoms)	Rituximab Gemticitabine Oxaliplatine (2 weeks)	Rituximab Bendamustine (3 months)	Rituximab Cyclophosphamide Adriamycin Vincristine Prednisone (2 weeks)	Rituximab (5 weeks)
IgG anti-S against SARS-CoV-2	Yes	Unknown	Unknown	Unknown
Admission during which bitherapy antiviral treatment was administered	1st	1st	1st	2nd
Previous antiviral treatment (days)	Nirmatrelvir/ritonavir (1º 4 days) (2º 5 days)	Nirmatrelvir/ ritonavir (1º 5 days) (2º 5 days)	Nirmatrelvir/ritonavir (5 days)	Nirmatrelvir/ritonavir (5 days)
Virus variant at the onset of symptoms	Omicron BQ.1.1 (sequenced)	Omicron BA.5.2 (sequenced)	Omicron BQ.1.1.4 (sequenced)	Omicron BA.5.2 (sequenced)
Virus variant before bitherapy treatment	Omicron BA.2, BA.4 or BA.5[a]	Omicron BA.5.2 (sequenced)	Unknown	Omicron BA.5.2 (sequenced)
Ct prior to starting antiviral bitherapy	22	21	11	25
Days from symptom onset to administration of biotherapy treatment	23	74	16	199
Days from end of last antiviral treatment to starting antiviral bitherapy	11	10	9	194
Oxygen therapy at the time of biotherapy treatment	Room air (FiO_2 21%)	Room air (FiO_2 21%)	Nasal cannula (FiO_2 28%)	Room air (FiO_2 21%)
Maximum oxygen after bitherapy treatment	Room air (FiO_2 21%)	Room air (FiO_2 21%)	Helmet CPAP (FiO_2 60%)	Room air (FiO_2 21%)
Days of systemic corticosteroid treatment before definitive antiviral treatment	No	No	30	No
COVID-19 pneumonia	No	No	Yes	Yes
SARS-CoV-2 vaccination schedule	2 doses	2 doses	2 doses + 1 booster	2 doses
CLINICAL OUTCOMES				
Admission to ICU after administration of bitherapy treatment	No	No	Yes[c]	No
Hospital readmission after bitherapy treatment	Yes[b]	No	No	No
Days from initiation of bitherapy treatment to RT-PCR negative result	6	5	–	–
Death after administration of bitherapy treatment	Yes[b]	No	Yes[d]	No
Days of follow-up from last hospital discharge to end of study[e]	130	159	16	110

Abbreviations: CPAP, continuous positive airway pressure; DLBCL, diffuse large B-cell lymphoma; FiO2, inspiratory oxygen fraction; mAbs, monoclonal antibodies; ICU, intensive care unit.

[a]Obtained by "VIASURE SARS-CoV-2 Varian III Real Time PCR Detection Kit", a rapid test that detected the existence of the Q954H gene and the absence of the A2710T gene (high probability of being an Omicron BA.2, BA.4 or BA.5 variant; this gene is common to all three).

[b]The patient was admitted for progression of hematologic malignancy on March 7, 2023, with no clinical suspicion of persistence or recurrence of SARS-CoV-2 infection. On April 4, 2023 (4 months after RT-PCR negativation) he died due to his hematologic disease.

[c]Admission to the ICU during treatment with antiviral bitherapy.

[d]Died due to progression of respiratory failure secondary to SARS-CoV-2 infection.

[e]We consider 5/24/2023 as the current date.

they did not present symptoms related to COVID-19. In short, three of the four patients were not readmitted, nor did they die as a result of progression or relapse of the infection, nor did they require new antiviral treatment, and the infection was considered resolved. In addition, within a short period of time, the RT-PCR was negative for the first time (cases 1 and 2 6 and 5 days after the start of bitherapy, respectively; case 3 died and did not recur and case 4 did not have a control RT-PCR). Table 1 shows in more detail the clinical characteristics and the results obtained.

Despite being a very vulnerable group of patients, with previous failure to nirmatrelvir/ritonavir and on treatment with rituximab-based therapeutic schemes, 3 of the 4 patients responded satisfactorily after the administration of nirmatrelvir/ritonavir and remdesivir bitherapy. The remaining patient had a poor evolution, but it must be taken into account how advanced the disease was at the time of bitherapy administration. In short, the results obtained propose a new therapeutic alternative for oncohematological patients with difficulty in eliminating the virus. However, further studies are necessary to confirm this hypothesis.

FUNDING

None to declare

CONFLICT OF INTEREST

Authors declare no conflict of interest.

REFERENCES

1. Calderón-Parra J, Múñez-Rubio E, Fernández-Cruz A, et al. Incidence, Clinical Presentation, Relapses and Outcome of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Patients Treated With Anti-CD20 Monoclonal Antibodies. Clin Infect Dis. 2022;74(10):1786-1794. doi: 10.1093/cid/ciab700.
2. Choi B, Choudhary MC, Regan J, et al. Persistence and Evolution of SARS-CoV-2 in an Immunocompromised Host. N Engl J Med. 2020;383(23):2291-2293. doi: 10.1056/NEJMc2031364.
3. Tang X, Feng YM, Ni JX, et al. Early Use of Corticosteroid May Prolong SARS-CoV-2 Shedding in Non-Intensive Care Unit Patients with COVID-19 Pneumonia: A Multicenter, Single-Blind, Randomized Control Trial. Respiration. 2021;100(2):116-126. doi: 10.1159/000512063.
4. Martinez MA, Chen TY, Choi H, et al. Extended Remdesivir Infusion for Persistent Coronavirus Disease 2019 Infection. Open Forum Infect Dis. 2022;9(8):ofac382. Published 2022 Jul 29. 14 doi:10.1093/ofid/ofac382
5. Pérez Catalán I, García Muñoz S, Roig Martí C, Gómez Alfaro I, Serrano Picazo L, Torres García M, Reig Valero R, Ferrando Piqueres R, Mateu Campos L, Ramos Rincón JM, Usó Blasco J. Nirmatrelvir/ritonavir as a potential treatment for prolonged SARS-CoV-2 infection in immunocompromised patients. Rev Esp Quimioter. 2022 Dec;35(6):589-591. doi: 10.37201/req/078.2022.
6. Schultz DC, Johnson RM, Ayyanathan K, et al. Pyrimidine inhibitors synergize with nucleoside analogues to block SARS-CoV-2. Nature. 2022;604(7904):134-140. doi:10.1038/s41586-022-04482-x
7. Trottier CA, Wong B, Kohli R, Boomsma C, Magro F, Kher S, et al. Dual Antiviral Therapy for Persistent Coronavirus Disease 2019 and Associated Organizing Pneumonia in an Immunocompromised Host. Clinical Infectious Diseases. 2022 Oct 25;76(5):923–5.
8. Mikulska M, Sepulcri C, Dentone C, Magne F, Balletto E, Baldi F, et al. Triple combination therapy with two antivirals and monoclonal antibodies for persistent or relapsed SARS-CoV-2 infection in immunocompromised patients. Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America [Internet]. 2023 Mar 28 [cited 2023 Apr 26];ciad181. Available from: https://pubmed.ncbi.nlm.nih.gov/36976301/