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ORIGINAL PAPER

Neutralizing monoclonal antibodies in haematological patients paucisymptomatic for COVID-19: The GIMEMA EMATO-0321 study

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Summary

COVID-19 continues to be a relevant issue among patients with haematological malignancies (HM). Vaccines are frequently not effective in subjects on active treatment. In this multicentre retrospective study of Gruppo Italiano Malattie EMatologiche dell'Adulto (GIMEMA), we collected data from 91 paucisymptomatic HM patients treated with anti-spike neutralizing monoclonal antibodies (nMoAbs) to determine time to viral clearance, referencing it to the expected value of 28 days from an historical group of untreated paucisymptomatic

patients. Secondary endpoints included rate of hospitalization, intensive care unit (ICU) admission, COVID-19 related death and safety. SARS-CoV-2 molecular swab negativity was obtained in 86 patients (95%), with a median time of 18 days (IQR 13–26; $p < 0.0001$). We did not find significant variations according to age, diagnosis, treatment type, vaccination status or nMoAbs type. Rate of hospitalization due to COVID-19 progression was 12% (11/91), with 2 patients (2.2%) requiring ICU admission. With a median follow-up of 2.33 months, the overall mortality was 5.5% (5/91), with 3 deaths due to COVID-19. Side effects were rare and self-limiting. Our data suggest that nMoAbs can limit the detrimental effect of immunosuppressive treatments on COVID-19 clinical progression and time to viral clearance. The original trial was registered at www.clinicaltrials.gov as #NCT04932967.

KEYWORDS
COVID-19, haematological malignancies, neutralizing monoclonal antibodies, paucisymptomatic patients

INTRODUCTION

Patients with haematological malignancies (HM) infected with SARS-CoV-2 have a high risk of developing severe coronavirus disease (COVID-19) with an increased mortality.[1–3] In healthy subjects, mRNA vaccines were demonstrated to be effective in reducing COVID-19, in particular severe forms.[4,5] However, humoral and cellular response after two-dose vaccination is reduced in HM patients when compared to the general population.[6,7] This impaired immune response determines an ineffective viral clearance, which may favour prolonged infection, development of severe COVID-19 and also the appearance of SARS-CoV-2 variants.[8,9] These findings confirm the urgent need to find alternative strategies for treatment of overt infection. Anti-spike Neutralizing Monoclonal Antibodies (nMoAbs) are indicated for the treatment of paucisymptomatic individuals, with several phase 3 trials demonstrating a significant reduction of the risk of progression to severe COVID-19 and of median time to negativization.[10–13] However, HM subjects were excluded from randomized trials with consequent lack of information about efficacy and safety in this fragile population.

Given the well-known immunosuppressive status present in most HM patients on active treatment, we hypothesized that nMoAbs could have a high rationale in this setting. Therefore, we designed the multicentre retrospective study of Gruppo Italiano Malattie EMatologiche dell'Adulto (GIMEMA) EMATO0321 with the aim to evaluate the activity of different nMoAbs approved by the Agenzia Italiana del Farmaco (AIFA) in paucisymptomatic HM patients.

METHODS

Study design

We conducted a multicentre retrospective, observational study at 13 Italian sites, enrolling all consecutive patients with SARS-CoV-2 infection, documented by Reverse Transcription Polymerase Chain Reaction (RT-PCR) testing, and treated with nMoAbs from March to December 2021. Only paucisymptomatic HM patients on active treatment or within 6 months from therapy discontinuation were included. Paucisymptomatic definition required the presence of at least one COVID-19 symptom and no need for oxygen support or hospitalization due to COVID-19. Radiological evaluation with chest CT scan and/or chest x-rays was performed as clinically indicated, and the evidence of lung involvement was not considered an exclusion criterian due to more severe infection. As defined by AIFA, nMoAbs are indicated for the treatment of confirmed COVID-19 (within 10 days from symptom onset) in paucisymptomatic patients considered at high risk of progressing to severe infection. nMoAbs approved by AIFA include Bamlanivimab, Bamlanivimab/Etesevimab, Casirivimab/Imdevimab, Sotrovimab and Regdanvimab. The primary endpoint was to assess the time to SARS-CoV-2 RT-PCR negativity. Secondary endpoints consisted in evaluation of hospitalization rate due to COVID-19, intensive care unit (ICU) admission rate due to respiratory failure, mortality due to COVID-19 and safety profile. The trial was approved by the ethics committee at Istituto Nazionale dei Tumori in Milan (181/21) and by each participating centre and it was conducted in accordance with the Good Clinical Practice guidelines. All patients provided written informed consent. The study was designed to test a reduction in the time to SARS-CoV-2 RT-PCR test negativization, estimating a minimum sample size of 31 subjects to achieve 91% power to detect, at a 0.05 significance level, a reduction of 14 days. Calculation was performed with a one-sided, one-sample log-rank test considering an expected median time to negativization in patients treated with nMoAB of 14 days compared with a median value of 28 days in the historical group of paucisymptomatic HM patients not treated with nMoAbs from the Italian database (ITA-HEMA-COV) (data unpublished).

Statistical methods

Demographic and baseline data including disease characteristics were summarized descriptively. Categorical data were presented as frequencies and percentages. For continuous data, median and range were presented. Non-parametric tests were performed for comparisons among groups (chi-squared and Fisher exact test in case of categorical variables or response rate, Mann–Whitney and Kruskal-Wallis test in case of continuous variables). Wilcoxon signed rank test with continuity correction was used to the test the time to RT-PCR negativization *versus* the historical expected value defined into the study protocol. All tests were two-sided, accepting $p < 0.05$ as indicating a statistically significant difference and confidence intervals were calculated at 95% level. All analysis were performed using the R software [R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/]. Study data were collected and managed using REDCap electronic data capture tools hosted at GIMEMA Foundation.[14,15]

RESULTS

Patient characteristics

Overall, 91 HM patients (median age 61 years) were evaluated, with a median follow up of 2.3 months from nMoAb administration (range 0.19–9.57 months). The median age was 61 years (range 19–85), with 36 females and 55 males. The most frequent diagnoses were non-Hodgkin lymphoma, myeloproliferative neoplasms and multiple myeloma, with 33, 13 and 10 cases, respectively. Sixty-five of 91 patients were on active treatment, whereas 17 had completed their therapies within 6 months; only 4 were on a watch and wait strategy, and for 5 patients this data was missing. In 15 subjects, the last treatment was chemotherapy; in 19, immunochemotherapy; in 17, immunotherapy; in 11, target therapy; in 4, autologous stem cell transplantation; in 3, allogeneic stem cell transplantation; and in 2, chimeric antigen receptor (CAR) T-cell therapy. In 4 cases, the type of last treatment was not available. The immunochemoterapy group included subjects treated with anti CD20 monoclonal antibodies and chemotherapy drugs, whereas the immunotherapy groups included patients treated with anti CD20 monoclonal antibodies (50%), anti CD19 monoclonal antibodies (6%), anti CD38 monoclonal antibodies (12%), anti CD30 monoclonal antibodies (6%) or checkpoint inhibitors (12%). Ten, 33 and 29 subjects received one, two and three vaccine doses before SARS-CoV-2 infection respectively, whereas 19 patients did not receive any dose. Seventy of 72 vaccinated patients received a mRNA-vaccine, whereas 2 received and adenovirus-associated vaccine. The median absolute neutrophil count (ANC) in the entire population was 2860 cells/μl (range 10–16 460 cells/μl), whereas the median absolute lymphocyte count (ALC) in the entire cohort was 860 cells/μl (40–2650 cells/μl). The most frequent symptoms at COVID-19 onset were fever and cough, which were present in 62 and 60 patients, respectively. Detailed baseline characteristics are reported in Table 1. Fifty of 91 patients were treated with Bamlanivimab/Etesevimab, 28 with Casirivimab/Imdevimab, 6 with Sotrovimab, 4 with Bamlanivimab as single agent and in 4 patients the type of nMoAb was not available. Median time between SARS-CoV-2 positivity and nMoAb administration was 3 days [interquartile range (IQR) 2–4].

Time to viral clearance

SARS-CoV-2 RT-PCR negativization was obtained in 86 patients (95%), with a median time of 18 days (IQR 13–26). This is significantly lower in comparison to the expected value of 28 days reported in an historical group of paucisymptomatic Italian HM patients not treated with nMoAbs ($p < 0.0001$). Considering treatment subgroups, we did not find any significant variation in terms of time to viral clearance ($p = 0.83$). Moreover, we reported a median time to RT-PCR test negativization of 21 days (IQR 15–26) in the immunochemotherapy subgroup. Among patients vaccinated with at least one dose and unvaccinated patients the median time to viral clearance was 18 (IQR 12–26) and 20 days (range 14–29, $p = 0.41$), respectively. Moreover, we did not find any significant variation according to age, disease status, diagnosis, nMoAbs type in terms of median time to viral clearance (Table 2). Moreover, both ALC and ANC did not differ among patients who were able or failed to achieve molecular swab negativity (1470 cells/μl vs. 840 cells/μl and 3980 cells/μl vs. 2730 cells/μl, both $p > 0.05$, respectively).

Hospitalization rate

The hospitalization rate due to COVID-19 progression was 12% (11/91), with a low percentage of patients requiring ICU admission (2%, 2/91). As expected, hospitalization was less common in patients who achieved swab negativity compared to those who did not (8.9%, 8/86 vs. 60%, 3/5, $p = 0.012$), due to an increased risk of death with an ongoing infection. Moreover, we reported an increased, though not significant, median time to negativization in hospitalized compared to non-hospitalized patients [18 days (range 1–63) vs. 25 days (range 9–174), $p = 0.078$]. Ten of 11 hospitalized patients had lymphoproliferative malignancies (6 non-Hodgkin lymphoma, 2 chronic lymphocytic leukaemia and 2 multiple myeloma patients). We did not report a significant variation according to vaccination status (at least one dove vs not vaccinated) in terms of hospitalization rate (16% 3/19, vs. 11%, 8/72, $p = 0.69$). Of note, considering different treatment subgroups, the highest hospitalization rate was reported among patients treated with immunotherapy with 4 cases (24%) (2 subjects treated with rituximab and 2 treated with daratumumab). We did

TABLE 1 Characteristics of paucisymptomatic patients with haematological malignancies

Characteristic	*N* = 91
Age	62 (19–85)
Sex	
Male	55 (60%)
Female	36 (40%)
Diagnosis	
NHL	33 (36%)
HL	6 (6.7%)
CLL	7 (7.8%)
MM	10 (11%)
WM	2 (2.2%)
AML	9 (10%)
ALL	3 (3.4%)
CML	3 (3.4%)
MPN Ph neg	13 (14%)
Other	5 (5.5%)
Response status	
CR	51 (60%)
PR	21 (25%)
PD	7 (8.2%)
Diagnosis	6 (7.1%)
Unknown	6
Haematological therapy	
Active	65 (76%)
Prior	17 (20%)
WW	4 (4.7%)
Unknown	5
Type of last treatment	
CT	15 (17%)
Immunotherapy	17 (20%)
ImmunoCT	19 (22%)
autoSCT	4 (4.6%)
alloSCT	3 (3.3%)
CAR T	2 (2.3%)
Target therapy	11 (13%)
Other	16 (18%)
Unknown	4
Last treatment line	
1	49 (54%)
>1	35 (38%)
WW	4 (4.4%)
Type of variant	
Alpha (B.1.1.7 and Q lineages)	5 (5.5%)
Delta (1.617.3)	5 (5.5%)
Other	6 (6.6%)
Unknown variant	75 (82.4%)
Symptoms at onset	
Fever	62 (68%)
Cough	60 (66%)
Ageusia/Disgeusia	14 (15%)
Pharyngodynia	14 (15%)
Asthenia	27 (30%)
Headache	13 (14%)
Myalgia	20 (22%)
GE Symptoms	7 (7.7%)
Dyspnea	10 (11%)
Tachypnea	1 (1.1%)
Anosmia	8 (8.8%)
Radiology images showing typical COVID pneumonia	
Yes	5 (5.5%)
No	86 (94.5%)
Type of nMoAbs	
Bamlanivimab/Etesevimab	50 (54.9%)
Casirivimab/Imdevimab	28 (30.7%)
Bamlanivimab	4 (4.4%)
Sotrovimab	6 (6.7%)
Unknown	3 (3.3%)
Vaccination status	
Not vaccinated	19 (21%)
1 dose received	10 (11%)
2 doses received	33 (36%)
3 doses received	29 (32%)

Abbreviations: NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; CLL, chronic lymphocytic leukaemia; MM, multiple myeloma; WM, Waldenstrom Macroglobulinemia; AML, acute myeloid leukaemia; ALL, acute lymphoblastic leukaemia; CML, chronic myeloid leukaemia; MPN Ph neg, myeloproliferative neoplasm Philadelphia negative; CR, complete response; PR, partial response, PD, progressive disease; WW, watch and wait strategy; CT, chemotherapy; immunoCT, immunochemotherapy; autoSCT, autologous stem cell transplantation; alloSCT, allogeneic stem cell transplantation; GE symptoms, gastrointestinal symptoms.

not find any impact on COVID-19 clinical progression according to vaccination status, disease status, type of nMoAb administered or type of treatment (Table 3).

COVID-19 related mortality

With a median follow up of 2.3 months, we reported 3 (3.3%) deaths due to COVID-19 and 2 (2.2%) due to progressive HM, leading to an overall mortality rate of 5.5%. Of note, all 3 deaths due to COVID-19 occurred in patients with lymphoproliferative diseases: in particular, 2 patients with non-Hodgkin lymphoma and 1 patient with chronic lymphocytic leukaemia.

TABLE 2 Median time to SARS-CoV-2 RT-PCR negativity

Characteristic	Number at risk	Median time days (IQR)	*p* value[a]
Overall population	86	18 (13–26)	
Age			
>60 years	44	18 (13–29)	0.95
<60 years	41	18 (14–26)	
Diagnosis			
NHL	33	18 (13–26)	0.62
HL	6	26 (17–46)	
CLL	7	14 (11–17)	
MM	10	14 (9–29)	
WM	2	34 (25–42)	
AML	9	19 (13–23)	
ALL	3	26 (22–27)	
CML	2	12 (12–16)	
MPN Ph neg	16	20 (18–26)	
Other	5	22 (12–29)	
Disease status			
CR	51	19 (13–26)	0.43
PR	21	14 (9–27)	
PD	7	15 (13–24)	
Diagnosis	6	24 (16–30)	
Type of last treatment			
CT	15	17 (12–28)	0.83
Immunotherapy	17	18 (14–29)	
ImmunoCT	19	21(15–26)	
autoSCT	4	14 (11–19)	
alloSCT	3	20(16–27)	
CAR T	2	21 (18–24)	
Target therapy	11	16 (12–20)	
Other	16	18 (11–20)	
Type of nMoAbs			
Bamlanivimab/ Etesevimab	50	18 (13–29)	0.64
Casirivimab/ Imdevimab	28	16 (12–26)	
Bamlanivimab	4	27 (18–28)	
Sotrovimab	6	22 (16–26)	
Unknown	3	20 (20–20)	
Vaccination status			
Not vaccinated	19	20 (14–29)	0.41
At least one dose	72	18 (12–26)	

Abbreviations: IQR, interquartile range; NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; CLL, chronic lymphocytic leukaemia; MM, multiple myeloma; WM, Waldenstrom Macroglobulinemia; AML, acute myeloid leukaemia; ALL, acute lymphoblastic leukaemia; CML, chronic myeloid leukaemia; MPN Ph neg, myeloproliferative neoplasm Philadelphia negative; CR, complete response; PR, partial response, PD, progressive disease; CT, chemotherapy; autoSCT, autologous stem cell transplantation; alloSCT, allogeneic stem cell transplantation.

[a]Kruskal-Wallis rank sum test.

Safety profile

All nMoAbs were administered in an outpatient setting, and no patients required hospitalization for the management of adverse events. The most frequent side effects included fever (4.4%), chills (4.4%) and diarrhoea (3.3%) (Table 4).

DISCUSSION

HM patients have an increased mortality rate, ranging from 34% to 37% in the pre-vaccine era,[1,2] and mRNA-based vaccines are frequently ineffective in patients on active treatment.[6,7] Therefore, it is essential to urgently implement an effective treatment to limit the risk of COVID-19 progression in the setting of overt infection.

In this multicentre, retrospective observational trial, we gave the proof of concept of the efficacy of nMoAbs in the setting of patients with an altered immune system due to their malignancies and subsequent treatments. We demonstrated how the early use of nMoAbs in paucisymptomatic patients can decrease the time to viral clearance compared to an historical control group composed of paucisymptomatic HM patients not treated with nMoAbs.

The median interval between COVID-19 diagnosis and nMoAb administration of 3 days reported in our study is shorter than the one of randomized trials.[12,13,16] Several pivotal studies stressed the clinical relevance of an early nMoAb use in order to prevent the progression of infection.[17]

Considering the impact of nMoAbs on time to viral clearance according to different types of treatments, the median time of 21 days to swab negativity observed in patients treated with immunochemotherapy should be positively read. In fact, this population is considered at high risk for more severe and protracted COVID-19 course,[18] due to iatrogenic immunosuppression that can be potentially nullified by nMoAbs administration.

Interestingly, we did not find any association between ALC and/or ANC and probability to obtain a swab negativity after nMoAbs. This finding supports the hypothesis that, in this setting, nMoAbs are potentially able to overwhelm the immunodeficiency related to specific anticancer treatments.

We observed a low percentage (12%) of patients with a progressive infection requiring hospitalization. Our result compares well with literature data. In particular, Weinbergerová et al. reported a hospitalization rate of 17% in HM patients treated with bamlanivimab as single agent or with casirivimab/imdevimab.[19] Of note, almost one third of their patients were completely asymptomatic at the moment of nMoAb administration. On the contrary, in our study all subjects included were paucisymptomatic.

Interestingly, with a median follow-up of 2.3 months, in this high-risk population we reported an overall mortality of 5.5%, with only 3 deaths related to SARS-CoV-2 infection. In the EPICOVIDEHA study conducted during the first two

TABLE 3 Rate of hospitalization due to COVID-19 in patients with haematological malignancies

Characteristic	Number at risk	Hospitalization due to COVID-19 *n* (%)	*p* value[a]
Overall population	91	11 (12%)	
Swab negativity achievement			
No	5	3 (60%)	0.012
Yes	86	8 (9.3%)	
Diagnosis			
NHL	33	5 (15%)	0.27
HL	6	0 (0%)	
CLL	7	2 (29%)	
MM	10	2 (20%)	
WM	2	1 (50%)	
AML	9	0 (0%)	
ALL	3	0 (0%)	
CML	2	0 (0%)	
MPN Ph neg	16	0 (0%)	
Other	5	1 (20%)	
Disease status			
CR	51	5 (9.8%)	0.31
PR	21	2 (9.5%)	
PD	7	0 (0%)	
Diagnosis	6	2 (33%)	
Unknown	6	2 (33%)	
Type of last treatment			
CT	15	2 (13%)	0.32
Immunotherapy	17	4 (24%)	
ImmunoCT	19	1 (5.3%)	
autoSCT	4	1 (25%)	
alloSCT	3	0 (0%)	
CAR T	2	0 (0%)	
Target therapy	11	2 (18%)	
Other	16	0 (0%)	
Unknown	4	1 (25%)	
Type of nMoAbs			
Bamlanivimab/ Etesevimab	50	4 (8%)	0.64
Casirivimab/Imdevimab	28	5 (18%)	
Bamlanivimab	4	1 (25%)	
Sotrovimab	6	0 (0%)	
Unknown	3	1 (33%)	
Vaccination status			
Not vaccinated	19	3 (16%)	0.69
At least one dose	72	8 (11%)	

Abbreviations: NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; CLL, chronic lymphocytic leukaemia; MM, multiple myeloma; WM, Waldenstrom Macroglobulinemia; AML, acute myeloid leukaemia; ALL, acute lymphoblastic leukaemia; CML, chronic myeloid leukaemia; MPN Ph neg, myeloproliferative neoplasm Philadelphia negative; CR, complete response; PR, partial response, PD, progressive disease; CT, chemotherapy; autoSCT, autologous stem cell transplantation; alloSCT, allogeneic stem cell transplantation.

[a]Fisher's exact test; Wilcoxon rank sum test.

TABLE 4 Neutralizing monoclonal antibodies' most frequent side effects

Characteristic	Number at risk
Fever	4 (4.4%)
Chills	4 (4.4%)
Headache	3 (3.3%)
Nausea or Emesis	2 (2.2%)
Myalgia	1 (1.1%)

pandemic waves, HM patients with initially mild COVID-19 had a mortality rate of 16.7%.[20] Our study is not able to exclude the potential protective role of vaccination and other antiviral treatments, however the protective impact of nMoAbs on early mortality among seronegative subjects has been recently demonstrated by a randomized trial.[21]

All 3 deaths related to COVID-19 occurred in patients with lymphoproliferative diseases, once again highlighting the increased infective risk of these subjects despite the advent of efficacious preventive strategies and effective treatments.

In conclusion, our results support the hypothesis that early nMoAb administration in paucisymptomatic HM patients can effectively shorten the duration of infection. Our finding of 18 days as median time to negativization should be positively read, because it may allow to maintain the dose intensity of anti-cancer treatment and may also hamper the emergence of viral variants during long lasting infections. The promising results in preventing COVID-19 clinical progression should be further evaluated in future prospective trials.

AUTHOR CONTRIBUTION

VM, LP, FP and PC designed the study and wrote the manuscript; AG, ML, EC, and PF helped design the study; AP did the statistical plan, analysis and interpreted the data; All the authors recruited participants and collected and interpreted data. All authors contributed to manuscript writing and review of the manuscript.

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CONFLICTS OF INTEREST

All the authors have no disclosures to declare for this submitted paper.

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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REFERENCES

1. Passamonti F, Cattaneo C, Arcaini L, Bruna R, Cavo M, Merli F, et al. Clinical characteristics and risk factors associated with COVID-19 severity in patients with haematological malignancies in Italy: a retrospective, multicentre, cohort study. Lancet Haematol. 2020;7:e737–45. https://doi.org/10.1016/S2352-3026(20)30251-9
2. Vijenthira A, Gong IY, Fox TA, Booth S, Cook G, Fattizzo B, et al. Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. Blood. 2020;136:2881–92. https://doi.org/10.1182/blood.2020008824
3. Garcíá-Suárez J, De La Cruz J, Cedillo Á, Llamas P, Duarte R, Jiménez-Yuste V, et al. Impact of hematologic malignancy and type of cancer therapy on COVID-19 severity and mortality: lessons from a large population-based registry study. J Hematol Oncol. 2020;13:1–12. https://doi.org/10.1186/S13045-020-00970-7/TABLES/4
4. El Sahly HM, Baden LR, Essink B, Doblecki-Lewis S, Martin JM, Anderson EJ, et al. Efficacy of the mRNA-1273 SARS-CoV-2 vaccine at completion of blinded phase. N Engl J Med. 2021;385:1774–85. https://doi.org/10.1056/NEJMOA2113017/SUPPL_FILE/NEJMOA2113017_DATA-SHARING.PDF
5. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020;383:2603–15. https://doi.org/10.1056/nejmoa2034577
6. Pimpinelli F, Marchesi F, Piaggio G, Giannarelli D, Papa E, Falcucci P, et al. Fifth-week immunogenicity and safety of anti-SARS-CoV-2 BNT162b2 vaccine in patients with multiple myeloma and myeloproliferative malignancies on active treatment: preliminary data from a single institution. J Hematol Oncol. 2021;14:81. https://doi.org/10.1186/s13045-021-01090-6
7. Marasco V, Carniti C, Guidetti A, Farina L, Magni M, Miceli R, et al. T-cell immune response after mRNA SARS-CoV-2 vaccines is frequently detected also in the absence of seroconversion in patients with lymphoid malignancies. Br J Haematol. 2021;196: 548–58. https://doi.org/10.1111/bjh.17877
8. Corey L, Beyrer C, Cohen MS, Michael NL, Bedford T, Rolland M. SARS-CoV-2 variants in patients with immunosuppression. N Engl J Med. 2021;385:562–6. https://doi.org/10.1056/NEJMSB2104756/SUPPL_FILE/NEJMSB2104756_DISCLOSURES.PDF
9. Kemp SA, Collier DA, Datir RP, Ferreira IATM, Gayed S, Jahun A, et al. SARS-CoV-2 evolution during treatment of chronic infection. Nature. 2021;592:277–82. https://doi.org/10.1038/s41586-021-03291-y
10. Gottlieb RL, Nirula A, Chen P, Boscia J, Heller B, Morris J, et al. Effect of Bamlanivimab as monotherapy or in combination with Etesevimab on viral load in patients with mild to moderate COVID-19: a randomized clinical trial. JAMA. 2021;325:632–44. https://doi.org/10.1001/JAMA.2021.0202
11. Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGEN-COV antibody combination and outcomes in outpatients with Covid-19. N Engl J Med. 2021;385:e81. https://doi.org/10.1056/NEJMOA2108163/SUPPL_FILE/NEJMOA2108163_DATA-SHARING.PDF
12. Gupta A, Gonzalez-Rojas Y, Juarez E, Crespo Casal M, Moya J, Falci DR, et al. Early treatment for Covid-19 with SARS-CoV-2 neutralizing antibody Sotrovimab. N Engl J Med. 2021;21:1941–50. https://doi.org/10.1056/NEJMOA2107934/SUPPL_FILE/NEJMOA2107934_DATA-SHARING.PDF
13. Chen P, Nirula A, Heller B, Gottlieb RL, Boscia J, Morris J, et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. N Engl J Med. 2021;384:229–37. https://doi.org/10.1056/NEJMOA2029849/SUPPL_FILE/NEJMOA2029849_DATA-SHARING.PDF
14. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42:377–81. https://doi.org/10.1016/J.JBI.2008.08.010
15. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inform. 2019;95:103208. https://doi.org/10.1016/J.JBI.2019.103208
16. Jenks JD, Aslam S, Horton LE, Law N, Bharti A, Logan C, et al. Early monoclonal antibody administration can reduce both hospitalizations and mortality in high-risk outpatients with coronavirus disease 2019 (COVID-19). Clin Infect Dis. 2022;74:752–3. https://doi.org/10.1093/CID/CIAB522
17. Callaway E. COVID antibody drugs work best when given as early as possible. Nature. 2022 March 30. Epub ahead of print. https://doi.org/10.1038/d41586-022-00893-y
18. Gaitzsch E, Passerini V, Khatamzas E, Strobl CD, Muenchhoff M, Scherer C, et al. COVID-19 in patients receiving CD20-depleting Immunochemotherapy for B-cell lymphoma. HemaSphere. 2021;5(7):e603. https://doi.org/10.1097/HS9.0000000000000603
19. Weinbergerová B, Demel I, Víšek B, Válka J, Čerňan M, Jindra P, et al. Successful early use of anti-SARS-CoV-2 monoclonal neutralizing antibodies in SARS-CoV-2 infected hematological patients – a Czech multicenter experience. Hematol Oncol. 2022; 40(2): 280–286. https://doi.org/10.1002/hon.2974
20. Pagano L, Salmanton-García J, Marchesi F, Busca A, Corradini P, Hoenigl M, et al. COVID-19 infection in adult patients with hematological malignancies: a European Hematology Association survey (EPICOVIDEHA). J Hematol Oncol. 2021; 14(1):168. https://doi.org/10.1186/S13045-021-01177-0
21. Abani O, Abbas A, Abbas F, Abbas M, Abbasi S, Abbass H, et al. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2022;399:665–76. https://doi.org/10.1016/S0140-6736(22)00163-5

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