New Microbiologica, 45, 1, 62-72, 2022, ISSN 1121-7138

FULL PAPER

Convalescent plasma for haematological patients with SARS-CoV-2 pneumonia and severe depletion of B-cell lymphocytes following anti-CD20 therapy: a single-centre experience and review of the literature

Alessandra Oliva[1], Francesca Cancelli[1], Andrea Brogi[1], Ambrogio Curtolo[1], Giulia Savelloni[1], Guido Siccardi[1], Giulia Marcelli[2], Laura Mazzuti[3], Paolo Ricci[2], Ombretta Turriziani[3], Guido Antonelli[3], Mario Venditti[1], Claudio M. Mastroianni[1]

[1]*Department of Public Health and Infectious Diseases, Sapienza University of Rome;*
[2]*Department of Radiological Sciences, Sapienza University of Rome;*
[3]*Department of Molecular Medicine, Laboratory of Virology, Sapienza University of Rome*

SUMMARY

Convalescent plasma (CP) therapy might be effective in patients with haematological malignancies and B-cell depletion. We report a single-centre experience of COVID-19 patients with non-Hodgkin lymphoma and absence of B-cells as a consequence of anti-CD20 therapy successfully treated with CP from October 2020 to May 2021. CP was given in the presence of pneumonia with respiratory failure despite standard treatment and consisted of three infusions on an alternate-day basis. A review of the current literature on this topic was also performed. Six patients were identified (median age 59.5 years (range 50-73)). The last anti-CD20 drug administration occurred 60 days before infection (range 0-360). CP was administered after a median of 51 days (range 9-120) from SARS-CoV-2 diagnosis, with an early improvement in all but one subject. We suggest a possible clinical benefit of convalescent CP treatment in COVID-19 patients with haematological malignancies and B-cell depletion having persistent/recurrent pneumonia.

Received January 20, 2022 *Accepted* February 15, 2022

INTRODUCTION

Patients with haematological malignancies have a higher risk of developing severe SARS-CoV-2 pneumonia and overall mortality appears to be high (Vijenthira *et al*., 2020). Amongst them, those treated with anti-CD20 drugs may present with a very low number, if not absence, of B-cell lymphocytes, leading to a lack of antibody development (Sacco *et al*., 2018; Malsy *et al*., 2020; Clark *et al*., 2020). In this challenging scenario, providing virus-specific neutralizing antibodies by means of convalescent plasma (CP) of recovered SARS-CoV-2 patients may represent a promising rescue option (Senefeld *et al*., 2021). Nevertheless, convalescent plasma showed no substantial effect on overall survival in patients with COVID-19 pneumonia (Omrani *et al*., 2019; Chauhan *et al*., 2021; Bégin *et al*., 2021; Bartoletti *et al*., 2022), although some results are still controversial (Avendaño-Solá *et al*., 2021; Franchini *et al*., 2021).

Patients with haematological malignancies are rarely included in clinical trials. In this regard, very few data have been reported so far on the potential effect of CP in haematological patients with severe SARS-CoV-2 infection and absence of B-cells following anti-CD20 drugs and, therefore, definite evidence on its efficacy in this specific subgroup of patients is still lacking (Furlan *et al*., 2021a).

Herein, we describe a single-centre preliminary experience of patients with non-Hodgkin lymphoma (NHL) and complete depletion of B-cells as a consequence of anti-CD20 therapy subsequently treated with CP for persistent/recurrent COVID-19 pneumonia.

Key words:
SARS-CoV-2, COVID-19, convalescent plasma, haematological malignancy, non-Hodgkin lymphoma, anti-CD20 therapy, B-cell depletion.

Corresponding author:
Alessandra Oliva
E-mail: alessandra.oliva@uniroma1.it

MATERIALS AND METHODS

Patients

From October 2020 to May 2021, a retrospective observational study including patients with haematological malignancies and severe depletion of B-cells

as a consequence of anti-CD20 drugs treated with CP was performed. All patients were hospitalized at the Infectious Diseases Department of Policlinico Umberto I, Sapienza University of Rome because of SARS-CoV-2 infection.

Nasopharyngeal swab samples were collected and SARS-CoV-2 RNA was detected by using real time RT-PCR assay (RealStar SARS-CoV2 RT-PCR, Altona Diagnostics). SARS-CoV-2 RNA from plasma samples was extracted using Total purification RNA kit (Norgen Biotek Corp.) after virus concentration by centrifugation at high speed (14,000 rpm for 3 hours at 4°C). Ten µl of extracted RNA was reverse-transcribed and simultaneously amplified using a real-time RT-PCR system (FTD, Siemens Healthineers) targeting N gene and ORF1ab region. A result was reported as SARS-CoV-2 positive when Ct value was <40.

Inclusion criteria were:

1) adult patients with haematological malignancies and severe/complete B-cell depletion;
2) having received or receiving anti-CD20 therapy;
3) absence of SARS-CoV-2 specific antibodies and
4) SARS-CoV-2 pneumonia with respiratory failure requiring oxygen supplementation despite the best treatment available at the time.

Patients with haematological malignancies not receiving anti-CD20 drugs were excluded from the study; however, when treated with CP for SARS-CoV-2 pneumonia, clinical features and outcomes of these subjects were recorded (*Supplementary Table 1*). Patients receiving anti-CD20 therapy for conditions other than haematological malignancies were also excluded (*Figure 1*). The study was approved by the local Ethics Committee (ID Prot. 109/2020). All patients agreed to data collection and gave informed written consent for CP infusion.

Convalescent plasma treatment

All subjects underwent the same CP protocol, consisting of a total of three infusions (each 300 ml) on an alternate-day basis. The time of CP administration was based on each patient's clinical and radiological conditions. As per institutional protocol, all patients also received remdesivir, corticosteroids and low molecular weight heparin (LMWH) whereas antibiotics were given only in the presence of suspected or documented super-infections. CP was collected and stored in accordance with the European programme of COVID-19 convalescent plasma collection and transfusion (https://ec.europa.eu/health/blood_tissues_organs/covid-19_en).

RESULTS

Clinical characteristics of the patients are summarized in *Table 1*, whereas features and outcomes of patients with haematological malignancies not fulfilling inclusion criteria but treated for CP are de-

Table1 - *Characteristics of the haematological patients with SARS-CoV-2 pneumonia and severe depletion of B-cell lymphocytes following anti-CD20 therapy treated with convalescent plasma.*

Case (age/ sex)	*Type of malignancy*	*Type of anti-CD20 drug/ time since last administration*	*Hypogammaglobulinemia*	*Duration of SARS-CoV-2 NP° positivity before CP, days*	*Plasma SARS-CoV-2 RNA before CP, Ct**	*Previous SARS-CoV-2 therapy*	*B-cell, cell/ mmc*	*Specific antibodies before CP*	*Time of improvement from CP administration, days*	*Time of negativity of plasma SARS-CoV-2 RNA after last CP dose, days*	*Adverse events*	*Duration of NP positivity, days*	*Outcome*
#1 (56, F)	NHL (MCL)	RTX (4 days)	Yes	120	32	CSC, RDV	0	Absent	4	16	No	170	Survived
#2 (68, F)	NHL	RTX (10 months)	Yes	65	36.9	CSC, RDV	0	Absent	5	1	No	116	Survived
#3 (50, F)	NHL (FL)	OBI (2 months)	Not performed	37	37	CSC, RDV	0	Absent	4	Not performed	No	68	Survived
#4 (63, F)	NHL	RTX (current)	Yes	65	33	CSC, RDV	0	Absent	9	6	No	114	Survived
#5 (73, F)	NHL	RTX (2 months)	Not performed	13	Not detectable	CSC, RDV	0	Absent	No	Not performed	No	42	Died**
#6 (50, F)	NHL	RTX (12 months)	Yes	9	39	CSC, RDV	0	Absent	3	Not performed	Transient sinus tachycardia	37	Survived

MCL: Mantle cell lymphoma; FL: follicular lymphoma; RTX: rituximab; OBI: Obinutuzumab; NHL: non-Hodgkin's lymphoma; CSC: corticosteroids; RDV: remdesivir; NP: nasopharyngeal; CP: convalescent plasma. °: NP swabs were analysed with FTD SARS-CoV-2 test (Siemens Healthineers) for the qualitative detection of SARS-CoV-2 RNA. *: SARS-CoV-2 RNA from plasma samples was extracted using Total purification RNA kit (Norgen Biotek Corp.) after virus concentration by centrifugation at higher speed (14000 rpm for 3 hours at 4°C) and expressed as Ct, cycle threshold. **: cause of death was bacterial superinfection

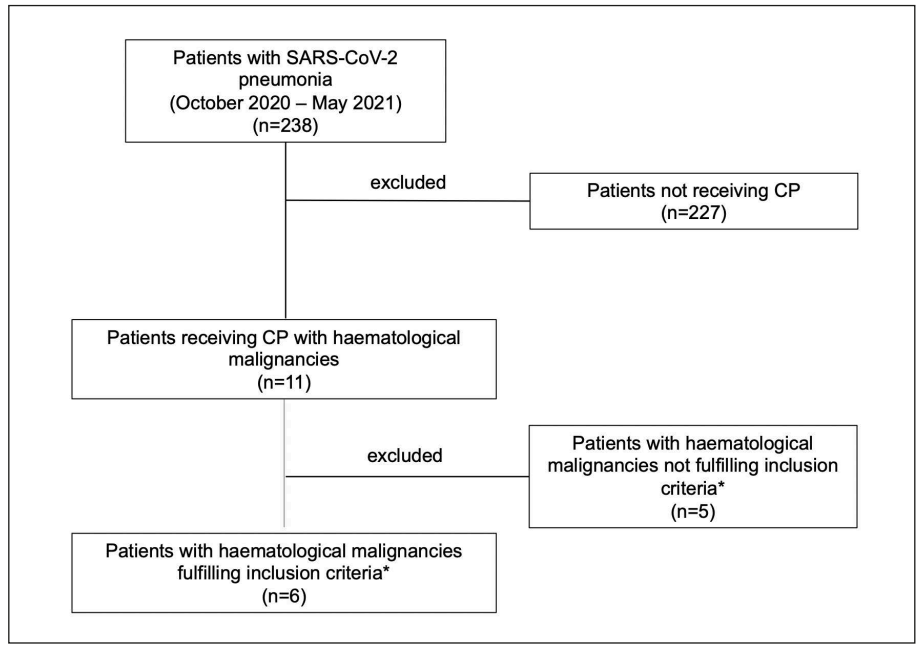

Figure 1 - Flow-chart of the study. *CP: convalescent plasma. *inclusion criteria were 1) adult patients with haematological malignancies and severe/complete B-cell depletion, 2) having received or receiving anti-CD20 therapy, 3) absence of SARS-CoV-2 specific antibodies and 4) SARS-CoV-2 pneumonia.*

picted in Supplementary *Table 1*. Overall, six female patients with NHL were identified, with a median age of 59.5 years (range 50-73). Five out of six received rituximab with the last anti-CD20 drug administration a median of 60 days before SARS-CoV-2 infection (range 0-360). CP was administered after a median of 51 days (range 9-120) from SARS-CoV-2 diagnosis, with an early improvement of clinical and respiratory conditions in all but one subject. Survival was observed in five subjects.

The detailed clinical course of ***case #1*** is depicted in *Figure 2*. A 56-year-old woman with mantle cell lymphoma and treated with rituximab-containing regimens (last administration 4 days before), developed dry cough and her nasopharyngeal (NP) swab was positive for SARS-CoV-2 on 28th October 2020 (day 0). On day 3, she developed fever and worsening of pulmonary gas exchanges, with a chest Computed Tomography (CT) on day 7 revealing the presence of multi-lobular pulmonary infiltrations. Despite treatment with remdesivir, dexamethasone and LMWH, she required high oxygen supplementation over the following days. Her conditions gradually improved and she was discharged on day 48. On day 62, the patient presented to the Emergency Department (ED) with a ten-day fever. Lymphocyte subset testing showed absence of B cells. A new chest CT revealed a worsening condition (*Figure 2*). Empiric antibiotic therapy was started; however, with all cultures being negative, antibiotics were discontinued and trimethoprim/sulfamethoxazole was given for 14 days, with slight improvement. On day 93 a worsening of respiratory conditions was again observed, as demonstrated by a new CT (*Figure 2*). Broncho-alveolar lavage (BAL) tested negative for all pathogens with the exception of SARS CoV-2. Plasma SARS-CoV-2 RNA was also detected, whereas SARS-CoV-2 antibodies and B-cells were absent. Therefore, on day 96 the patient was given a second 10-day course of remdesivir and, in the absence of improvement, CP was administered on days 120-122-124, with early (96 hours) clinical and radiological amelioration (*Table 1*). Subsequent plasmatic RNA was substantially reduced and SARS-CoV-2 antibodies became detectable. The patient was discharged on day 127 on good clinical conditions. On day 140 plasma RNA was cleared and NP swab resulted negative only at day 170.

Case #2 was a 68-year-old woman with NHL (last rituximab-containing regimens in March 2020) who tested positive for SARS-CoV-2 at a screening NP swab on 30th December 2020 (day 0). On day 27, she presented to the ED with a 1-day history of fever and dry cough. At admission, the patient was in good clinical condition, febrile. Lymphocyte subset testing showed severe depletion of B-cells (1/μL). Although pulmonary gas exchanges were fairly good, a chest CT scan showed bilateral lung infiltrations that involved roughly 30% and 10% of left and right pulmonary parenchyma, respectively. Due to a progressive worsening of pulmonary gas exchanges requiring supplemental oxygen, a 5-day course of remdesivir was started, with, however, a progressive deterioration of clinical and respiratory conditions, as showed by a new CT scan performed on day 62. Based on positive plasma SARS-CoV-2 RNA (Ct 36.9), absence of both B-cells and SARS-CoV-2 antibodies, CP was infused on days 65-67-69 (*Table1*). The patient's clinical conditions and pulmonary gas exchanges improved within 5 days with plasma RNA testing negative at day 70. She was discharged on

day 73, with NP swab RT-PCR turning negative on day 93.

Case #3, a 50-year-old woman with NHL and on maintenance treatment with obinutuzumab (last administration January 2021) presented to the ED on 3rd March 2021 (day 0) because of fever and fatigue. Her NP swab tested positive for SARS-CoV-2, whereas CT scan revealed no pulmonary alterations. At admission, her vital signs were normal, with lymphocyte subset testing showing severe depletion of B-cells (8/μL). The patient underwent a 5-day course of remdesivir treatment and was discharged in good clinical conditions on day 21. However, on day 29 she was again admitted to ED because of 3-day fever and respiratory failure requiring high oxygen supplementation. A new CT scan showed involvement of the right lower pulmonary lobe. Lymphocyte subset assays showed absence of B-cells. SARS-CoV-2 RNA was detected on BAL and plasma (37 Ct) and SARS-CoV-2 antibodies were absent. Therefore, on days 37-39-41 the patient underwent CP treatment, with clinical and radiological improvement (*Table 1*). On day 51, the patient was discharged in good conditions. Her NP swab tested still positive at follow-up visit on day 68.

Case #4 was a 63-year-old woman with extra-nodal NHL since 2014, currently in maintenance therapy with rituximab. A screening NP swab prior to rituximab treatment tested positive for SARS-CoV-2 on 22nd February 2021 (day 0). On day 7 she developed fever, which lasted for 3 days. On day 53 she presented to the ED because of the new appearance of fever, fatigue and respiratory distress. At admission, her clinical conditions were compromised with respiratory failure requiring non-invasive-ventilation. A chest CT scan revealed the presence of mul-

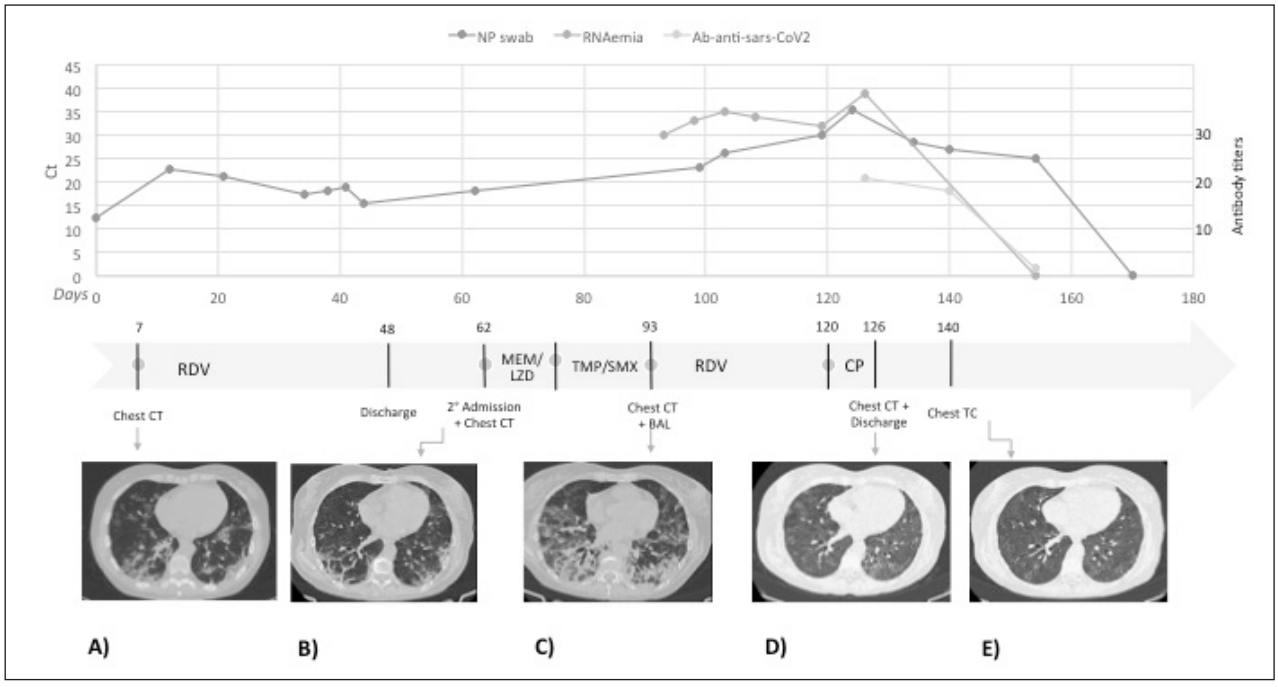

Figure 2 - *Timeline of clinical, radiological and therapeutic course of case #1. A) CT scan (day 7): Total lung involvement was about 40%; the CT features were typical for COVID-19 pulmonary interstitial pneumonia, with a peripheral and multifocal appearance and predilection of lower lobes and posterior segments. In the superior lobes a ground glass aspect was prevalent, while crazy paving areas, interstitial septal thickening superimposed to ground glass opacities, were more appreciable in the inferior lobes. In the right lower lobe, traction bronchiectasis was evident. B) CT scan (day 62): a worsening of interstitial pneumonia with a total lung involvement of about 70% was observed. Consolidations were still appreciated in the lower lobes, while in the upper lobes an improvement of crazy paving extension was evident. C) CT scan (day 93): a sudden worsening with wide consolidative opacities in the lower lobes was observed; total lung involvement increased to 75%. D) CT scan (day 126): nearly complete resolution of the consolidative areas, increase of the ground glass opacities (as observed at the late stage of the disease) and appearance of some linear parenchymal bands and architectural distortions were observed. Three small round bronchiectasis, with wall thickening, were also appreciated. E) CT scan (day 140): a further improvement was observed, with a nearly total resolution of consolidative opacities and total involvement of lung parenchyma by pure ground glass areas was reduced to 10%.*

RDV: remdesivir; MEM: meropenem; LNZ: linezolid; TMP/SMX: trimethoprim/sulfamethoxazole; CP: convalescent plasma; BAL: broncho-alveolar lavage; NP: nasopharyngeal.

ti-lobular pulmonary infiltrates that involved more than 50% of total lung parenchyma. Thus, a 5-day remdesivir plus dexamethasone course was prescribed. Blood analyses showed absence of B-cells and SARS-CoV-2 antibodies whereas plasma SARS-CoV2 RNA was detectable (33 Ct). Based on these data, on days 65-67-69 the patient underwent CP treatment. Her clinical conditions and pulmonary gas exchanges gradually improved, with progressive weaning from oxygen supplementation. SARS-CoV-2 RNA was cleared from plasma but remained present on NP swab. The patient was discharged on day 105 in good clinical condition and NP swab turned negative on day 115.

Case #5, a 73-year-old woman with a history of NHL under chronic rituximab (last infusion two months before admission) presented to ED on 7th April 2021 (day 0) because of fever and fatigue. At hospital admission her NP swab was positive for SARS-CoV-2. Gas exchanges were good and a chest CT was negative for parenchymal lesions. Given the history of haematological malignancy, the patient was hospitalized for clinical monitoring. On day 6, clinical respiratory condition worsened, requiring oxygen supplementation, and a new chest CT disclosed multi-lobular pulmonary infiltrates (20% of pulmonary parenchyma). At blood examination, lymphocyte subset showed absence of B-cells, as well as SARS-CoV-2 antibodies and SARS-CoV-2 RNA in plasma. Despite a treatment course with remdesivir and dexamethasone followed by CP (*Table 1*), the patient required mechanical ventilation and on day 42 died as a consequence of multidrug-resistant gram-negative infection.

Case #6, on 10th May (day 0), three months after BNT162b2 m-RNA vaccine, a 50-year-old nurse in complete remission from an NHL presented to the ED for fever and dry cough. Her last treatment with rituximab was one year before. On admission, NP swab tested positive for SARS-CoV-2 and chest CT revealed bilateral infiltrates involving approximately 40% of the pulmonary parenchyma. Laboratory blood analyses showed the absence of B-cells and SARS-CoV-2 antibodies; SARS-CoV-2 RNA was detectable in plasma (39 Ct). Despite a remdesivir plus dexamethasone treatment course, progressive respiratory deterioration prompted to CP administration on days 9-11-13 (*Table 1*). The patient's conditions improved within 72 hours and she was discharged on day 15. NP turned negative on day 37.

DISCUSSION

Patients with haematological malignancies are a group vulnerable to SARS-CoV-2 due to prolonged and severe immunosuppression resulting from both chemo-immunotherapy and the underlying disease (Sacco *et al.*, 2018; Clark *et al.*, 2020; Senefeld *et al.*, 2021). Furthermore, mortality rates in these patients are worryingly high (Vijenthira *et al.*, 2020).

In particular, subjects being treated with anti-CD20 therapy experience a marked and often prolonged hypogammaglobulinemia and/or lymphopenia with a delayed reconstitution of innate and adaptive immunity (Shishido *et al.*, 2012; Ferrari *et al.*, 2021; Hueso *et al.*, 2020). Consequently, these patients are unable to mount an efficient antibodies production and antimicrobial response, remaining therefore not only at increased risk of acquiring opportunistic infections but also, when infected, more prone to a fatal outcome (Baang *et al.*, 2021; Hensley *et al.*, 2021). With regard to SARS-CoV-2 infection, this leads to:

1) inability to produce specific antibodie;
2) prolonged shedding of viral RNA from the upper respiratory tract and
3) long-lasting severe symptoms (Shishido *et al.*, 2012; Ferrari *et al.*, 2021; Hueso *et al.*, 2020; Baang *et al.*, 2021; Hensley *et al.*, 2021).

In this context, CP from patients who had fully recovered after SARS-CoV-2 infection may be effective by providing virus-specific neutralizing antibodies and therefore resulting in direct clearance of the disease (Ferrari *et al.*, 2021; Delgado-Fernández *et al.*, 2021; Focosi *et al.*, 2021; Luetkens *et al.*, 2020). CP has been successfully used in other viral infections such as SARS, influenza A or Ebola (Burnouf *et al.*, 2014; Hung *et al.*, 2009; Cheng *et al.*, 2005) and therefore, based on these previous experiences, its use has also been suggested for patients with SARS-CoV-2 (Diorio *et al.*, 2020).

However, results from randomized clinical trials on the addition of CP to standard treatment have been disappointing: overall, although some benefits in terms of reduced disease progression (Wang *et al.*, 2021) or prevention of progression to non-invasive or invasive ventilation or death at 28 days (Avendaño-Solá *et al.*, 2021) have been observed, no reduction in mortality rates has been reported in patients with SARS-CoV-2 pneumonia (Omrani *et al.*, 2019; Chauhan *et al.*, 2021; Bégin *et al.*, 2021; Menichetti *et al.*, 2021; Simonovich *et al.*, 2021; RECOVERY Collaborative Group 2021). Furthermore, adverse events occurred more frequently in patients treated with CP than in those treated with the standard of care (Bégin *et al.*, 2021; Menichetti *et al.*, 2021; Simonovich *et al.*, 2021; RECOVERY Collaborative Group 2021).

Nevertheless, none of the abovementioned studies specifically investigated the impact of CP on patients suffering from haematological malignancies, whereas a subgroup analysis of a recent study seemed to show a potential benefit in patients receiving an immunosuppressive treatment or having an immunosuppressive disease who are unable to mount effective immune responses (Writing Committee for the REMAP-CAP Investigators *et al.*, 2021). Likewise, a Bayesian analysis from the RECOVERY trial suggest-

ed that SARS-CoV2 seronegative patients could benefit from CP even though no benefits were observed on the overall enrolled population (Hamilton, 2021). Since the current available therapeutic armamentarium for COVID-19 has been further enriched with antiviral drugs and monoclonal antibodies, with the latter commonly used in immunocompromised seronegative subjects, the role of CP may be reduced even in this setting. However, a therapeutic benefit of CP treatment in patients with primary antibody deficiency has recently been observed even months after infection (Lang-Meli J *et al.,* 2022), suggesting that CP may possibly still retain a role for immunocompromised seronegative patients with refractory or persistent pneumonia (Beraud M *et al.,* 2022). As a matter of fact, the current guidelines recognize that, although CP is not recommended for the treatment of COVID-19 in hospitalized patients without impaired humoral immunity (Bartoletti *et al.,* 2022; COVID-19 Treatment Guidelines, 2021), there is still insufficient evidence to recommend either for or against the use of COVID-19 CP for the treatment of COVID-19 in hospitalized patients with impaired humoral immunity (COVID-19 Treatment Guidelines, 2021), raising the debate on whether CP may give some benefits in this special population.

The data available so far regarding the use of CP in haematological patients under anti-CD20 drugs derive mainly from small studies, case series or case reports (Malsy *et al.,* 2020; Baang *et al.,* 2021; Hensley *et al.,* 2021; Delgado-Fernández *et al.,* 2021; Honjo *et al.,* 2020) and seem to support the hypothesis that CP therapy might be an effective option in these patients (Senefeld *et al.,* 2021; Ferrari *et al.,* 2021; Hueso *et al.,* 2020; Baang *et al.,* 2021; Honjo *et al.,* 2020; Avanzato *et al.,* 2020; Moore *et al.,* 2020; Tremblay *et al.,* 2020; London *et al.,* 2021; Schenker *et al.,* 2021; Zimmerli *et al.,* 2021; Weinbergerova *et al.,* 2021; Basheer *et al.,* 2021; Erber *et al.,* 2021; Furlan *et al.,* 2021b), either to cure (Malsy *et al.,* 2020; Clark *et al.,* 2020; Ferrari *et al.,* 2021; Hueso *et al.,* 2020; Delgado-Fernández *et al.,* 2021; Thompson *et al.,* 2021; Avanzato *et al.,* 2020; Moore *et al.,* 2020; Tremblay *et al.,* 2020; London *et al.,* 2021; Schenker *et al.,* 2021; Zimmerli *et al.,* 2021; Weinbergerova *et al.,* 2021; Basheer *et al.,* 2021; Erber *et al.,* 2021; Furlan *et al.,* 2021b; Betrains *et al.,* 2020; Kenig *et al.,* 2021; Lancman *et al.,* 2020; Martinot *et al.,* 2020; McKemey *et al.,* 2021; Reuken *et al.,* 2021; Szwebel *et al.,* 2021; Wright *et al.,* 2021; Rnjak *et al.,* 2021; Ormazabal *et al.,* 2021), to prevent relapse of disease, or to obtain eradication of the virus (Gharbharan et al., 2021) (*Table 2*). In line with these observations, a recent case-control study showed that CP treatment was associated with improved 30-day mortality (Thompson *et al.,* 2021). Most of the seronegative patients in whom CP was used worsened late after first detection of SARS-CoV-2 infection and required multiple hospitalizations (Baang *et al.,* 2021; Hensley *et al.,* 2021; Schenker *et al.,* 2021; Zimmerli *et al.,* 2021; Weinbergerova *et al.,* 2021; Basheer *et al.,* 2021; Erber *et al.,* 2021; Furlan *et al.,* 2021b; Rnjak *et al.,* 2021; Ormazabal *et al.,* 2021), leading to a wide interval from disease clinical presentation to CP administration (*Table 2*).

Patients with haematological malignancies often experience prolonged shedding of viral RNA from the upper respiratory tract, and, in line with this, duration of viral positivity in our literature search ranged from 33 to 268 days (Thompson *et al.,* 2021; Sepulcri *et al.,* 2021; Hughes *et al.,* 2021). This phenomenon might be of significant concern since it seems to contribute to the selection of sequence SARS-CoV-2 variants within the same host, thus leading to the emergence of potentially infective viral subspecies (Baang *et al.,* 2021; Hensley *et al.,* 2021; Avanzato *et al.,* 2020; Sepulcri *et al.,* 2021; Lang-Meli J *et al.,* 2022).

All our patients had a relevant immunocompromised state with absence of B-lymphocytes as a consequence of rituximab/obinutuzumab treatment, experienced a worsening of respiratory conditions late after the first detection of SARS-CoV-2 infection requiring, in three cases, a second hospitalization, and had a documented persistency of viral detection in the absence of bacterial or fungal super-infections. CP was administered after a median of 51 days from symptoms onset, and, unlike the wide variability observed in the literature (*Table 2*), according to a predetermined protocol (Ferrari *et al.,* 2021; RECOVERY Collaborative Group 2021). This schedule of CP treatment was well-tolerated and provided significant clinical improvement and survival in all but one patient.

Although not frequently detected, the presence of SARS-CoV-2 RNA in plasma has been found as associated with more severe outcome (Xu *et al.,* 2021; Hogan *et al.,* 2021). In our case series, all but one patient had SARS-CoV-2 RNA positivity in plasma before CP administration, confirming that viral clearance from the blood in this special population may not occur or may be delayed as compared with other patients. Unfortunately, we were able to follow the plasma RNA trend in only three patients. Nevertheless, we confirmed SARS-CoV-2 RNA clearance from blood following CP in all these patients, possibly suggesting a therapeutic role of CP to this end.

Our report seems to confirm that in a specific subgroup of hospitalized patients with haematological malignancies and COVID-19 pneumonia (i.e., those with absence of B-cells as a result of anti-CD20 drugs and persistent symptoms of infection), the use of CP may contribute to faster viral clearance, prerequisite of an earlier clinical improvement (Avivi *et al.,* 2013; Long *et al.,* 2020; Lang-Meli J *et al.,* 2022; Beraud M *et al.,* 2022). Accordingly, CP may still retain a therapeutic role in an era where antiviral drugs and monoclonal antibodies have represented an important advance in the treatment of the disease.

Table 2 - *Review of the literature regarding haematological patients with SARS-CoV-2 pneumonia and severe depletion of B-cell lymphocytes following anti-CD20 therapy treated with convalescent plasma*

Ref.	*Type of study/ N of pts*	*Type of malignancy*	*Type of anti-B therapy/last administration*	*Duration of SARS-CoV-2 symptoms before plasma, days*	*SARS CoV2 Viremia/ duration of SARS NF swab*	*Previous SARS-CoV-2 therapy*	*B-cell, cell/mm^3*	*Specific antibodies before plasma*	*Mode of plasma administration*	*Time of improvement*	*Adverse events*	*Outcome*
Hueso et al., 2020	Case series/ 15 out of 17	DLBCL (n=4), MCL (n=3) FL (n=3) CLL, Richter syndrome (n=3) MZL (n=1) Waldenstrom macroglobulinemia (n=1)	RTX/OBI (15/17)*, CART (1) Median 4 months (3-6)*	56 (7-83)*	9 pts/Not specified	11 [IDQ (5), TOCI (4), CSC (8), RDV (3), LPV/r (2)]*	0 *	Absent*	2 consecutive units	Defervescence 48h Weaning from oxygen 5 days (1-45) Reduction of viremia in all 9 patients	No	Survived (n=16) Died (n=1) for bacterial superinfection*
Ormazabal Velez et al., 2021	Case report	NH FL	RTX	85**	NP/99	CSC, IDQ, TOCI	<0.1%	Absent	Single dose	Not applicable (pt was asymptomatic, plasma was used for preventing 3rd relapse)	No	Survived
Ormazabal Velez et al., 2021	Case report	MCL	RTX (2 months)	78, 108**	NP/190	CSC, IDQ, LPV/r, TOCI, ANAKIRNA, RDV	<0.1%	Absent	2 doses (day 78, 108)	Not applicable (pt was asymptomatic, plasma was used for eradication of the virus)	Infusion related minor skin hypersensitivity allergic reaction	Survived
Malsy et al., 2020	Case report	FL	OBI (2 months)	90 (1st course), 110 (2nd course)	Yes/131	RDV (10 days 1st cycle), RDV (5 days 2nd cycle)	0	Absent	2 units per day administered every other day (total 2 courses)	Not applicable (plasma was used for prevention of 2nd relapse) Viremia undetectable	No	Survived
Baang et al., 2021	Case report	MCL	CD3-CD20 bsAb (ongoing)	31, 112	NP/156	2 cycles of 10-days RDV	NP	Absent	Not s pecified	24 h (defervescence), gradual oxygen weaning	No	Survived
Bertrains et al., 2020	Case series/5	BL, DLBCL, PTLD, PMBCL (n=4)	RTX (n=5), median 8 months (4-15) CART (n=1), Anti-CD37 (n=1)	56 (47-116)	NP/ 103 (54–139)	CSC (n=1), IDQ (n=3), Azithromycin (n=1), RDV (n=2)	0	Absent	2 consecutive units (all units had a neutralising antibody titre of 1:160)	Clinical response (n=4)	No	Survived (n=4) Died (n=1) due to invasive aspergillosis
Sepulcri et al., 2021	Case report	MCL	RTX	88	Yes/268	DRV/r, IDQ, CSC, TOCI, RDV (3 cycles), IVIG	NP	Absent	Not specified	Not specified	No	Died
Clark et al., 2020	Case report	orbital and meningeal MZL	RTX (1 month)	50	NP/57	LPV/r, CSC	3	Absent	2 units of 200 ml per day (2 days)	Defervescence, weaning from oxygen (24h)	No	Survived
Delgado-Fernandez et al., 2021§	Case report 1	primary cutaneous MZL, MCL (n=1),	RTX (3 months)	36	NP/51	TOCI, CSC	NP	Absent	1 unit of 300 ml 4 days apart	Reduction of oxygen (48h from 1st dose), weaning from oxygen (24h from 2nd dose)	Mild decrease Oxygen saturation, Fever	Survived
Delgado-Fernandez et al., 2021§	Case report 2	FL	RTX (1 month)	56	NP/63	IDQ, AZT	2	Absent	1 unit of 300 ml	24h (defervescence)	Mild decrease Oxygen saturation	Survived
Ferrari et al., 2021	Case series/7	FL (n=2), indolent NHL (n=1), SCT (n=2), DLBC (n=1), CLL (n=1)	RTX (n=7) Median 8 weeks (1-676)	55 (range 42-70)	NP/ median 77 days (range 56-147)	IDQ, CSC (n=7), IVIG (n=1)	NP	Absent	3 infusions (each 210 mL) on an alternate day basis (n=7)	48-72h (n=7)	No	Survived (n=7)
Honjo et al., 2020	Case report	CLL	OBI (23 days)	33	NP/36	IDQ, IVIG	NP	Absent	1 dose of 218 mL (3.6 mL/kg)	48h	No	Survived
Hughes et al., 2021	Case report	FL	CD3-CD20 bsAb	80	NP/112	No	NP	Absent	Two units	24h	No	Survived
Kenig et al., 2021	Case series/8	5/8 MZL (n=1), BL (n=1), FL (n=2), CLL (n=1)	RTX (n=3) (10-30 days), OBI (n=2) (30 days)	median 40 (range 7-60)	NP/unknown (n=2), 47-60->45	RDV +/- CSC	NP	Absent (4/5)	2 units in a 24 h interval	Not specified	No	Survived

Ref.	*Type of study/ N of pts*	*Type of malignancy*	*Type of anti-B therapy/last administration*	*Duration of SARS-CoV-2 symptoms before plasma, days*	*SARS CoV2 Viremia/ duration of SARS NF swab*	*Previous SARS-CoV-2 therapy*	*B-cell, cell/mm^3*	*Specific antibodies before plasma*	*Mode of plasma administration*	*Time of improvement*	*Adverse events*	*Outcome*
Lancman et al., 2020	Case report	B-ALL	RTX	1 (after reactivation)[#]	NP/>=10 (after reactivation)	IDQ, AZT, RDV, CSC	NP	Absent	2 units	48h	No	Survived
Martinot	Case report	CLL	RTX (6 months)	61	Yes (3.94log10 copies/ml)/103	IDQ, CSC, RDV	NP	Absent	200ml every 24h	Rapid improvement Viremia undetectable	No	Survived
Moore et al., 2020	Case report	NHL	OBI (37 days)	88	NP/>74	No	NP	Absent	One unit (200 ml)	Improvement	No	Survived
Reuken et al., 2021	Case report	FL	RTX (17 days)	125	NP/120	RDV, Infliximab	0	Absent	2 units 72h apart	Yes (extubation after 5 days)	No	Survived
Rniak et al., 2021	Case report	Nasopharyngeal DLBCL	RTX (5 w)	48, 105	Yes/>100	CSC, RDV	0	Absent	6 units (days 48-49, 54-57), 2 units (105, 109)	Yes Reduction of viremia	No	Survived
Szwebel et al., 2021	Case report	B-cell lymphoma	RTX first, OBI+Ibrutinib then (2 months)	65	Yes/Not specified	CSC, LPV/r, TOCI	NP	Absent	one dose every 24 h (2 units)	Yes (rapid improvement) Viremia undetectable	No	Survived
Wright et al., 2021	Case report	FL	RTX (few d)	Around 28	NP/Not specifed	AZT, IDQ	NP	NP	1 unit	Yes (72 h)	No	Survived
Gharbharan et al., 2021	Case series/15 out of 25	DLBCL (n=5), FL (n=3), MCL (n=2), CLL (n=2), transformed low grade lymphoma (n=1), PTLD (n=1), B-ALL (n=1)	RTX (n=21), OBI (n=1), Ocrelizumab (n=1), Blinatumomab (n=1), none (n=1)***	median 26 (IQR 15-34) ***	NP/Not specified[†]***	CSC (n=16), RDV (n=11), TOCI (n=1) ***	0 (n=10), 0.03x10^9/L (n=1), 0.13x10^9/L (n=1), NP (n=13) ***	Absent***	Varying (1 CP transfusion, n=21; 2 CP transfusions, n=4) ***	Not specified***	Yes (anaphylactic reaction, n=1; worsening of hypoxemia, n=2; skin rash, n=1; increase in liver enzymes, n=1) ***	Survived (n=21), Died (n=4) ***
Schenker et al., 2021	Case report	CLL	RTX (2 months)	31	NP/35[#]	RDV, CSC	NP	Absent	2 unit of 200 ml	Yes (24h)	No	Survived[#]
Zimmerli et al., 2021	Case report	CLL	RTX (5 months)	72 (followed by other cycle 15 days apart)	NP/88	None	1	Absent	3x200 ml/donor	Yes (8 days)	Not specified	Survived
Weinbergerova et al., 2021	32	Acute leukemia (10), Lymphoma (10), MM (6), CLL (3), Chronic myelogenous leukemia (1), Polycythemia vera (1), Autoimmune leukopenia (1)	Not specified	Median 1 (range 0-287)	Not specified	RDV (32), CSC (15)	Not specified	Not specified	2 units/cycle (2 cycles=9; 3 cycles=2; 4 cycles=1)	Not specified	No	29 survived, 3 died
Basheer et al., 2021	Case report	Not specified	RTX	>25 (1st hospitalization)	NP/75	RDV, CSC (1st hospitalization); RDV, CSC, IVIG, ivermectin (2nd hospitalization)	0.1	Absent	2 units (1st hospitalization); 4 units (2nd hospitalization)	Yes (within 10 days)	Not specified	Survived
Erber et al., 2021	Case series/1 out of 6[&]	FL	RTX (28 days)	21	NP/42	RDV	Absent	Absent	5 units	Not specified	Not specified	Survived
Furlan e t al., 2021[b]	Case series/4	FL (2), DLBCL (2)	RTX (10-90 days)	37-67 (from 1st positivity)	1/33-77	RDV, CSC (1st hospitalization), prolonged RDV (2nd hospitalization)	<0.1 (1 NP)	Absent	3 doses (300 ml each) (2nd hospitalization)	Median1.5 days (range 1-2 days)		Survived

*Refers to all study population, which included also patients without haematological malignancies (n=2); **refers to stroke related to COVID; °: Yes refers to discharge after 1st plasma infusion, No refers to absence of improvement after 2nd plasma infusion. #: pt became negative at NF swab but experienced COVID-19 reactivation after almost 1 year. ***: Refers to all study population, which included also patients without haematological malignancies (n=10); †: isolation could be lifted at a median of 11 days (range 3-68) after CP. #: the patient experienced a subsequent a second episode of COVID-19 with the same virus strain. &: data in the table refer to the FL case. §: refers to a case series including a total of three patients, two of them with haematological malignancies and therefore included in the table. FL: follicular lymphoma; RTX: rituximab; OBI: Obinutuzumab; MCL: Mantle cell lymphoma; MM: multiple myeloma; BL: Burkitt lymphoma; DLBCL: diffuse large B-cell lymphoma; MZL: Marginal zone lymphoma; PTLD: post-transplant lymphoproliferative disorder; PMBCL: primary mediastinal B-cell lymphoma; NHL: non-Hodgkin's lymphoma; SCT: stem cell transplantation; CLL: chronic lymphocytic leukemia; B-ALL: B cell acute lymphoblastic leukemia. IDQ: Hydroxychloroquine; TOCI: tocilizumab; CSC: corticosteroids; RDV: remdesivir; LPV/r: lopinavir/ritonavir; DRV: darunavir; AZT: azithromycin; IVIG: Intravenous Immunoglobulin; CD3-CD20 bsAb: CD3-CD20 bispecific antibody; IQR: Interquartile Range; NF: nasopharynegeal; NP: not performed.

Several limitations should be acknowledged. First, we were unable to ascertain rates of hypogammaglobulinemia in all the patients. Second, we could not perform viral cultures or viability tests from persistently positive NP swabs and, therefore, the possible presence of variants could not have been detected. Third, antibodies titres were not systematically measured. Fourth, all the reported cases were treated before monoclonal antibodies entered the market and, hence, we could not evaluate whether these patients might also benefit from CP. Nevertheless, in our case series CP was administered late during the course of the disease in patients with persisting pneumonia as a rescue therapy when several other treatments had been ineffective, definitely later than the suggested time for the optimal use of monoclonal antibodies.

Our report possibly contributed to the identification of a subgroup of haematological patients who may benefit from CP administration. Furthermore, it may open the path to additional studies investigating the optimal timing of CP administration in this particular setting of patients.

In conclusion, we showed a rapid clinical improvement and a possible survival benefit in COVID-19 patients with haematological malignancies and B-cell depletion as a consequence of anti-CD20 therapy having persistent pneumonia treated with CP transfusion. These encouraging preliminary reports provide further rationale for randomised clinical trials of CP in COVID-19 patients with haematological malignancies and B-cell depletion.

Acknowledgements

The authors thank all medical and nursing staff for their contribution in the clinical management of the patients.

Declaration of conflicts of interest

This research did not receive any specific grant from funding agencies in the public, business, or not-for-profit sectors. The authors declare no conflicts of interest.

References

Avanzato V.A., Matson M.J., Seifert S.N., Pryce R., Williamson B.N., et al. (2020). Case Study: Prolonged Infectious SARS-CoV-2 Shedding from an Asymptomatic Immunocompromised Individual with Cancer. *Cell*. **183** (7), 1901-1912.e9. doi: 10.1016/j.cell.2020.10.049

Avendaño-Solá C., Ramos-Martínez A., Muñez-Rubio E., Ruiz-Antorán B., Malo de Molina R., et al. (2021). A multicenter randomized open-label clinical trial for convalescent plasma in patients hospitalized with COVID-19 pneumonia. *J Clin Invest*. 152740. doi: 10.1172/JCI152740. Epub ahead of print. PMID: 34473652.

Avivi I., Stroopinsky D., Katz T. (2013). Anti-CD20 monoclonal antibodies: beyond B-cells. *Blood Rev*. **27** (5), 217-223. doi: 10.1016/j.blre.2013.07.002

Baang J.H., Smith C., Mirabelli C., Valesano A.L., Manthei D.M., et al. (2021) Prolonged Severe Acute Respiratory Syndrome Coronavirus 2 Replication in an Immunocompromised Patient. *J Infect Dis*. **223** (1), 23-27. doi: 10.1093/infdis/jiaa666.

Bartoletti M., Azap O., Barac A., Bussini L., Ergonul O., Krause R., et al. ESCMID. (2022). COVID-19 living guidelines: drug treatment and clinical management. *Clin Microbiol Infect*. **28** (2), 222-238. doi: 10.1016/j.cmi.2021.11.007. Epub 2021 Nov 22. PMID: 34823008; PMCID: PMC8606314.

Basheer M., Saad E., Laskar O., Schuster O., Rechnitzer H., et al. (2021). Clearance of the SARS-CoV-2 Virus in an Immunocompromised Patient Mediated by Convalescent Plasma without B-Cell Recovery. *Int J Mol Sci*. **22** (16), 8902. doi: 10.3390/ijms22168902. PMID: 34445605; PMCID: PMC8396366.

Bégin P., Callum J., Jamula E., Cook R., Heddle N.M., et al. (2021). Convalescent plasma for hospitalized patients with COVID-19: an open-label, randomized controlled trial. *Nat Med*. https://doi.org/10.1038/s41591-021-01488-2

Beraud M., Goodhue Meyer E., Lozano M., Bah A., Vassallo R., Brown B.L. (2022). Lessons learned from the use of convalescent plasma for the treatment of COVID-19 and specific considerations for immunocompromised patients. *Transfus Apher Sci*. **13**, 103355. doi: 10.1016/j.transci.2022.103355. Epub ahead of print. PMID: 35063360; PMCID: PMC8757642.)

Betrains A., Godinas L., Woei-A-Jin S.H., Rosseels W., Herck Y.V., et al. (2020). Convalescent plasma treatment of persistent severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection in patients with lymphoma with impaired humoral immunity and lack of neutralising antibodies. *Bjh*. **192**, 1097-1105.

Burnouf T., Seghatchian J. (2014). Ebola virus convalescent blood products: where we are now and where we may need to go. *Transfus Apher Sci*. **51** (2), 120-125. doi: 10.1016/j.transci.2014.10.003.

Chauhan L., Pattee J., Ford J., Thomas C., Lesteberg K., et al. (2021). A Multi-center, Prospective, Observational-cohort controlled study of Clinical Outcomes following COVID-19 Convalescent plasma therapy in hospitalized COVID-19 patients. *Clin Infect Dis*. ciab834. doi: 10.1093/cid/ciab834. Epub ahead of print. PMID: 34549274.

Cheng Y., Wong R., Soo Y.O., Wong W.S., Lee C.K., et al. (2005). Use of convalescent plasma therapy in SARS patients in Hong Kong. *Eur J Clin Microbiol Infect Dis*. **24** (1), 44-46. doi: 10.1007/s10096-004-1271-9.

Clark E., Guilpain P., Filip L., Pansu N., Le Bihan C., et al. (2020). Convalescent plasma for persisting COVID-19 following therapeutic lymphocyte depletion: a report of rapid recovery. *Br J Haematol*. **190** (3), e154-e156. doi: 10.1111/bjh.16981

COVID-19 Treatment Guidelines available at https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/convalescent-plasma/ last update December 16, 2021.

Delgado-Fernández M., García-Gemar G.M., Fuentes-López A., Muñoz-Pérez M.I., Oyonarte-Gómez S., et al. (2021). Treatment of COVID-19 with convalescent plasma in patients with humoral immunodeficiency - Three consecutive cases and review of the literature. *Enferm Infecc Microbiol Clin* (Engl Ed). S0213-005X(21)00035-5. doi: 10.1016/j.eimc.2021.01.013.

Diorio C., Teachy D.T., Bassiri H. (2020). Convalescent Plasma for COVID-19: An Old Therapy for a Novel Pathogen. *The Hematologist*. **17** (4) doi: 10.1182/hem.V17.4.10407

Erber J., Wiessner J.R., Huberle C., Schneider J., Mijoĉević H., et al. (2021). Convalescent plasma therapy in B-cell-depleted and B-cell sufficient patients with life-threatening COVID-19 - A case series. *Transfus Apher Sci*. 103278. doi: 10.1016/j.transci.2021.103278. Epub ahead of print. PMID: 34548246; PMCID: PMC8447834.

Ferrari S., Caprioli C., Weber A., Rambaldi A., Lussana F. (2021). Convalescent hyperimmune plasma for chemo-immunotherapy induced immunodeficiency in COVID-19 patients with hematological malignancies. *Leuk Lymphoma*. 62 (6), 1490-1496. doi: 10.1080/10428194.2021.1872070

Focosi D., Franchini M. (2021) COVID-19 neutralizing antibody-based therapies in humoral immune deficiencies: A narrative review. *Transfus Apher Sci*. **60** (3), 103071. doi: 10.1016/j.transci.2021.103071

Franchini M., Corsini F., Focosi D., Cruciani M. (2021). Safety and Efficacy of Convalescent Plasma in COVID-19: An Overview of Systematic Reviews. *Diagnostics*. **11**, 1663. https://doi.org/10.3390/diagnostics11091663

Furlan A., Forner G., Cipriani L., Vian E., Rigoli R., et al. (2021a). COVID-19 in B Cell-Depleted Patients After Rituximab: A Diagnostic and Therapeutic Challenge. *Front Immunol.* **12**, 763412. doi: 10.3389/fimmu.2021.763412. PMID: 34804051; PMCID: PMC8595333.

Furlan A., Forner G., Cipriani L., Vian E., Rigoli R., et al. (2021b). Dramatic Response to Convalescent Hyperimmune Plasma in Association With an Extended Course of Remdesivir in 4 B Cell-Depleted Non-Hodgkin Lymphoma Patients With SARS-Cov-2 Pneumonia After Rituximab Therapy. *Clin Lymphoma Myeloma Leuk.* **21** (9), e731-e735. doi: 10.1016/j.clml.2021.05.013. Epub 2021 May 21. PMID: 34217677; PMCID: PMC8139434.

Gharbharan A., Geurtsvan Kessel C.H., Jordans C.C.E., Blaauw M., van der Klift M., et al. (2021). Effects of treatment of COVID-19 with convalescent plasma in 25 B-cell depleted patients. *Clin Infect Dis.* ciab647. doi: 10.1093/cid/ciab647. Epub ahead of print. PMID: 34293119.

Hamilton F.W., Lee T., Arnold D.T., Lilford R., Hemming K. (2021). Is convalescent plasma futile in COVID-19? A Bayesian re-analysis of the RECOVERY randomized controlled trial. Int J Infect Dis. **109**, 114-117. doi: 10.1016/j.ijid.2021.06.034. Epub 2021 Jun 19. PMID: 34157385; PMCID: PMC8214317.

Hensley M.K., Bain W.G., Jacobs J., Nambulli S., Parikh U., et al. (2021). Intractable COVID-19 and Prolonged SARS-CoV-2 Replication in a CAR-T-cell Therapy Recipient: A Case Study. *Clin Infect Dis*. ciab072. doi: 10.1093/cid/ciab072.

Hogan C.A., Stevens B.A., Sahoo M.K., Huang C., Garamani N., et al. (2021). High Frequency of SARS-CoV2 RNAemia and Association With Severe Disease. *Clin Infect Dis*. **72** (9), e291-e295. doi: 10.1093/cid/ciaa1054.

Honjo K., Russell R.M., Li R, Liu W., Stoltz R., et al. (2020). Convalescent plasma-mediated resolution of COVID-19 in a patient with humoral immunodeficiency. *Cell Rep Med*. **2** (1), 100164. doi: 10.1016/j.xcrm.2020.100164.

Hueso T., Pouderoux C., Péré H., Beaumont A.L., Raillon L.A., et al. (2020). Convalescent plasma therapy for B-cell-depleted patients with protracted COVID-19. *Blood.* **136** (20), 2290-2295. doi: 10.1182.

Hughes C.M., Gregory G.P., Pierce A.B., Druce J.D., Catton M., et al. (2021). Clinical illness with viable severe acute respiratory coronavirus virus 2 (SARS-CoV-2) virus presenting 72 days after infection in an immunocompromised patient. *Infect Control Hosp Epidemiol*. 1-3. doi: 10.1017/ice.2021.120.

Hung I.F., To K.K., Lee C.K., Lee K.L., Chan K., et al. (2011). Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. *Clin Infect Dis*. **52** (4), 447-56. doi: 10.1093/cid/ciq106

Kenig A., Ishay Y., Kharouf F., Rubin L. (2021). Treatment of B-cell depleted COVID-19 patients with convalescent plasma and plasma-based products. *Clin Immunol.* **227**, 108723. doi: 10.1016/j.clim.2021.108723

Lancman G., Mascarenhas J., Bar-Natan M. (2020). Severe COVID-19 virus reactivation following treatment for B cell acute lymphoblastic leukemia. *J Hematol Oncol.* **13** (1), 131. doi: 10.1186/s13045-020-00968-1.

Lang-Meli J., Fuchs J., Mathé P., Ho H.E., Kern L., Jaki L., et al. (2022). Case Series: Convalescent Plasma Therapy for Patients with COVID-19 and Primary Antibody Deficiency. J Clin Immunol. **42** (2), 253-265. doi: 10.1007/s10875-021-01193-2. Epub 2021 Dec 10. PMID: 34893946; PMCID: PMC8664001.

London J., Boutboul D., Lacombe K., Pirenne F., Heym B., et al. (2021). Severe COVID-19 in Patients with B Cell Alymphocytosis and Response to Convalescent Plasma Therapy. *J Clin Immunol*. **41** (2), 356-361. doi:10.1007/s10875-020-00904-5.

Long Q.X., Liu B.Z., Deng H.J., Wu G.C., Deng K., et al. (2020). Antibody responses to SARS-CoV-2 in patients with COVID-19. *Nat Med*. **26** (6), 845-848.

Luetkens T., Metcalf R., Planelles V., Zheng Y., Larragoite E.T., et al. (2020). Successful transfer of anti-SARS-CoV-2 immunity using convalescent plasma in an MM patient with hypogammaglobulinemia and COVID-19. *Blood Adv*. **4** (19), 4864-4868. doi: 10.1182/bloodadvances.2020002595

Malsy J., Veletzky L., Heide J., Hennigs A., Gil-Ibanez I., et al. (2020). Sustained response after remdesivir and convalescent plasma therapy in a B-cell depleted patient with protracted COVID-19. *Clin Infect Dis*. ciaa1637.doi:10.1093/cid/ciaa1637

Martinot M., Jary A., Fafi-Kremer S., Leducq V., Delagreverie H., et al. (2020). Remdesivir failure with SARS-CoV-2 RNA-dependent RNA-polymerase mutation in a B-cell immunodeficient patient with protracted Covid-19. *Clin Infect Dis*. ciaa1474. doi: 10.1093/cid/ciaa1474

McKemey E., Shields A.M., Faustini S.E., Hill H.J., Barnskaya A., et al. (2021). Resolution of Persistent COVID-19 After Convalescent Plasma in a Patient with B Cell Aplasia. *J Clin Immunol*. **41** (5), 926-929. doi: 10.1007/s10875-021-00996-7.

Menichetti F., Popoli P., Puopolo M., Spila Alegiani S., Tiseo G., et al. (2021). Effect of High-Titer Convalescent Plasma on Progression to Severe Respiratory Failure or Death in Hospitalized Patients With COVID-19 Pneumonia: A Randomized Clinical Trial. *JAMA Netw Open.* **4** (11), e2136246. doi: 10.1001/jamanetworkopen.2021.36246.

Moore J.L., Ganapathiraju P.V., Kurtz C.P., Wainscoat B. (2020). A 63-year-old woman with a history of nonhodgkin lymphoma with persistent sars-cov-2 infection who was seronegative and treated with convalescent plasma. *Am J Case Reports*. **21**, e927812. doi: 10.12659/ajcr.927812.

Omrani A.S, Zaqout A., Baiou A., Daghfal J., Elkum N., et al. (2021). Convalescent plasma for the treatment of patients with severe coronavirus disease 2019: A preliminary report. *J Med Virol*. 93 (3), 1678-1686. doi: 10.1002/jmv.26537.

Ormazabal Vélez I., Induráin Bermejo J.., Espinoza Pérez J, Imaz Aguayo L., et al. (2021). Two patients with rituximab associated low gammaglobulin levels and relapsed covid-19 infections treated with convalescent plasma. *Transfus Apher Sci*. **60** (3), 103104. doi: 10.1016/j.transci.2021.103104.

RECOVERY Collaborative Group. (2021). Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label platform trial. *Lancet*. **397**, 2049-2059.

Reuken P.A., Stallmach A., Pletz M.W., Brandt C., Andreas N., et al. (2021). Severe clinical relapse in an immunocompromised host with persistent SARS-CoV-2 infection. *Leukemia*. **35** (3), 920-923. doi: 10.1038/s41375-021-01175-8

Rnjak D., Ravlić S., Šola A.M., Halassy B., Šemnički J., et al. (2021). COVID-19 convalescent plasma as long-term therapy in immunodeficient patients? *Transfus Clin Biol*. S1246-7820(21)00065-3. doi: 10.1016/j.tracli.2021.04.004.

Sacco K.A., Abraham R.S. (2018). Consequences of B-cell-depleting therapy: hypogammaglobulinemia and impaired B-cell reconstitution. *Immunotherapy.* **10** (8), 713-728. doi: 10.2217/imt-2017-0178.

Schenker C., Hirzel C., Walti L.N., Zeerleder S.S., Andres M., et al. (2021). Convalescent plasma and remdesivir for protracted COVID-19 in a patient with chronic lymphocytic leukaemia: a case report of late relapse after rapid initial response. *Br J Haematol.* doi: 10.1111/bjh.17806. Epub ahead of print. PMID: 34458995.

Senefeld J.W, Klassen S.A, Ford S.K, Senese K.A, Wiggins C C, et al. (2021) Use of convalescent plasma in COVID-19 patient of immunosuppression. *Transfusion.* 10.1111/trf.16525. doi: 10.1111/trf.16525.

Sepulcri C., Dentone C., Mikulska M., Bruzzone B., Lai A., et al. (2021). The longest persistence of viable SARS-CoV-2 with recurrence of viremia and relapsing symptomatic COVID-19 in an immunocompromised patient - a case study. *medRxiv preprint*. doi.org/10.1101/2021.01.23.21249554

Shishido S.N., Varahan S., Yuan K., Li X., Fleming S.D. (2012). Humoral innate immune response and disease. *Clin Immunol*. **144**, 142-158.

Simonovich V.A., Burgos Pratx L.D., Scibona P., et al. (2021). A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia. *N Engl J Med*. **384** (7), 619-629. doi: 10.1056/NEJMoa2031304.

Szwebel T.A., Veyer D., Robillard N., Eshagh D., Canoui E., et al. (2021). Usefulness of Plasma SARS-CoV-2 RNA Quantification by Droplet-based Digital PCR to Monitor Treatment Against COVID-19 in a B-cell Lymphoma Patient. *Stem Cell Rev Rep*. **17** (1), 296-299. doi: 10.1007/s12015-020-10107-5.

Thompson M.A., Henderson J.P., Shah P.K., Rubinstein S.M., Joyner M.J., et al. (2021). Association of Convalescent Plasma Therapy With Survival in Patients With Hematologic Cancers and COVID-19. *JAMA Oncol.* doi: 10.1001/jamaoncol.2021.1799.

Tremblay D., Seah C., Schneider T., Bhalla S., Feld J., et al. (2020). Convalescent plasma for the treatment of severe COVID-19 infection in cancer patients. *C Med*. **9** (22), 8571-8578. doi: 10.1002/cam4.3457.

Vijenthira A., Gong Y., Fox T.A., Booth S., Cook G., et al. (2020). Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. *Blood*. **136** (25), 2881-2892. doi: 10.1182/blood.2020008824.

Wang Y., Huo P., Dai R., Lv X., Yuan S., et al. (2021). Convalescent plasma may be a possible treatment for COVID-19: A systematic review. *Int Immunopharmacol*. 91, 107262. doi: 10.1016/j.intimp.2020.107262

Weinbergerova B., Mayer J., Kabut T., Hrabovsky S., Prochazkova J., et al. (2021). Successful early treatment combining remdesivir with high-titer convalescent plasma among COVID-19-infected hematological patients. *Hematol Oncol*. 10.1002/hon.2908. doi: 10.1002/hon.2908. Epub ahead of print. PMID: 34396566; PMCID: PMC8426890.

Wright Z., Bersabe A., Eden R., Bradley J., Cap A. (2021). Successful Use of COVID-19 Convalescent Plasma in a Patient Recently Treated for Follicular Lymphoma. *Clin Lymphoma Myeloma Leuk*. **21** (1), 66-68. doi: 10.1016/j.clml.2020.06.012

Writing Committee for the REMAP-CAP Investigators. (2021) Effect of Convalescent Plasma on Organ Support–Free Days in Critically Ill Patients With COVID-19: A Randomized Clinical Trial. *JAMA*. **326** (17), 1690-1702. doi: 10.1001/jama.2021.18178.

Xu D., Zhou F., Sun W., Chen L., Lan L., et al. (2021). Relationship Between Serum Severe Acute Respiratory Syndrome Coronavirus 2 Nucleic Acid and Organ Damage in Coronavirus 2019 Patients: A Cohort Study. *Clin Infect Dis*. **73** (1), 68-75. doi: 10.1093/cid/ciaa1085.

Zimmerli A., Monti M., Fenwick C., Eckerle I, Beigelman-Aubry C., et al. (2021). Case Report: Stepwise Anti-Inflammatory and Anti-SARS-CoV-2 Effects Following Convalescent Plasma Therapy With Full Clinical Recovery. *Front Immunol*. **12**, 613502. doi: 10.3389/fimmu.2021.613502. PMID: 33968017; PMCID: PMC8097002.