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Outcome of SARS-CoV2 infection in hematopoietic stem cell transplant recipients for autoimmune diseases

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ABSTRACT

Hematopoietic stem cell transplant (HSCT) recipients may be at high risk of mortality from coronavirus disease 2019 (COVID-19). However, specific data on COVID-19 after treatment with HSCT in patients affected by autoimmune diseases (ADs) are still lacking.

In this multicenter observational study of the European Society for Blood and Marrow Transplantation (EBMT), clinical data on COVID-19 in 11 patients affected by severe ADs treated with HSCT (n = 3 allogeneic transplant; n = 8 autologous transplant) are reported. All patients were symptomatic during the initial phase of the SARS-CoV-2 infection. At screening, 5 patients reported upper respiratory symptoms, 3 patients had cough without oxygen requirement, and 6 patients exhibited extra-pulmonary symptoms. Four cases developed a lower respiratory tract disease (LRTD). Hospitalization was required in 6 cases, without necessity of intensive care unit (ICU) admission and/or ventilation/supplemental oxygen. Different interventions were adopted: remdesivir (n = 1), nirmatrelvir/ritonavir (n = 1), sotrovimab (n = 1), immunoglobulins (n = 1). At last follow-up, all patients are alive and had resolution of the infection.

The current analysis describing the mild-moderate course of COVID-19 in transplant recipients affected by ADs, similar to the course observed in ADs under standard treatments, provides useful information to support the

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delivery of HSCT programs in this field. Vaccination and new treatments available for SARS-CoV-2 may be useful to further minimize the risk of infection.

1. Introduction

Hematopoietic stem cell transplant (HSCT) recipients have a higher risk of mortality with Coronavirus disease 2019 (COVID-19) owing to profound immune dysregulation [1]. In the years of pandemic, great efforts have been made to collect data on the impact of COVID-19 in transplant recipients, from both autologous and allogeneic donors. Previously, the European Society for Blood and Marrow Transplantation (EBMT) published data on 382 transplant recipients (236 allogeneic HSCT, 146 autologous HSCT) diagnosed with COVID-19. Overall, 91% experienced symptomatic disease. The median time from transplant to COVID-19 was 16 months in allogeneic and 25 months in autologous HSCT recipients. Moreover, 83% developed lower respiratory tract disease (LRTD) and 22% were admitted to intensive care unit (ICU). Survival at 6-week from COVID-19 diagnosis was 78% and 72% in allogeneic and autologous HSCT recipients, respectively. By multivariable analysis, older age, need for ICU and moderate/high immunodeficiency index increased the risk of death; other factors such as underlying diagnosis, time from transplant, graft-versus host disease (GvHD), or ongoing immunosuppressive therapy (IST) did not seem to influence survival [2]. Overall, mortality rate was higher in adult HSCT recipients with critical disease at admission. Similarly, the Center for International Blood and Marrow Transplant Research (CIBMTR) analyzed 318 patients (184 allogeneic HSCT, 134 autologous HSCT) diagnosed with symptomatic COVID-19. Overall, disease severity was mild in 49% of patients, while it was severe in 14%. At 30-day after COVID-19 diagnosis, overall survival was 68% for allogeneic and 67% for autologous HSCT recipients [3].

Recent evidence-base, as developed across the international scientific research communities, explored HSCT as single one-off procedure to treat a variety of severe autoimmune diseases (ADs) and diseases at the intersection between autoimmune and autoinflammatory syndromes (i.e. Behçet's disease) [4,5]. Current EBMT guidelines recommends HSCT as a specific treatment of patients with ADs responding poorly or refractory to conventional treatments [6]. Multiple sclerosis (MS) and systemic sclerosis (SSc) cover around 80% of transplants performed for ADs [7], where HSCT has become an integral and standard-of-care part of treatment algorithms. Although the majority of MS patients with COVID-19 had mild disease [8,9], MS population risk for severe events (hospitalization, intensive care unit-ICU admission, and death) is twice the risk than the age- and sex-matched population, mainly related to higher disability score and comorbidities [10]. A residual increase of hospitalization risk was observed in patients on anti-CD20 therapies, and a decrease in people receiving interferon [10]. Moreover, MS patients seemed to be at higher risk for post-acute sequelae of COVID-19, mainly due to preexisting severe neurologic impairment or mental health problems [11]. Data from larger national and international registries suggest that patients with rheumatic and musculoskeletal diseases (RMDs) did not have an increased risk of developing COVID-19 or a worse prognosis compared to the general population per se [12–16]. However, RMD patients on high-dose corticosteroids had a higher risk of SARS-CoV-2 infection or hospitalization [14], and data from the French RMD COVID-19 cohort indicated an increased risk for severe infection in patients receiving mycophenolate mofetil or rituximab [17]. Overall, the risk of poor COVID-19 outcomes in RMD patients seems to be mediated by the presence of comorbidities, treatment with glucocorticoids or rituximab, and high disease activity [18]. Therefore, specific data on COVID-19 after treatment with HSCT in patients affected by ADs are needed.

2. Methods

This study is a prospective multicenter observational study analyzing EBMT registry data and additional information collected using a specific questionnaire, designed for the EBMT study on 'impact of COVID-19 on stem cell transplant recipients' [2]. All patients gave informed consent before enrolment. The Swedish central Ethical Board (EPM 2020–01731) approved the study and other approvals if required, were obtained according to national regulations. Criteria for inclusion in the study were a positive PCR for SARS-CoV-2 on nasopharyngeal swab regardless of symptoms in patients who have undergone an allogeneic or autologous HSCT for AD as main indication at any time before the diagnosis of COVID-19. All diagnosis of ADs, as reported in the EBMT registry, have been included. Patients transplanted for a malignant hematological disease with a concomitant AD were excluded from the analysis. For this analysis, patients diagnosed with SARS-CoV-2 infection between March 2020 and May 2022 were included.

Questions included the symptoms at the time of diagnosis, previous COVID-19 vaccination history, potential risk factors for development of severe forms of infection (ie former smoker, dyslipidemia, high blood pressure, pulmonary arterial hypertension, diabetes, interstitial lung disease, use of steroid and/or immunosuppressive drugs, graft-versus-host disease -GvHD), the need for hospitalization, intensive care, treatment and outcome. In addition to the COVID-19 specific forms, the EBMT registry's so-called Minimal Essential Data A (MED-A) was used to extract previously submitted data regarding baseline patient information, data regarding the underlying diagnosis, and the transplant procedure, which were used in the analysis.

The primary objective of this study was to evaluate the epidemiology and outcome of AD patients with COVID-19 after HSCT. The characteristics of patients were reported by descriptive statistics. Median, minimum and maximum values were used for continuous variables, while absolute and percentage frequencies were used for categorical variables. Lower respiratory tract disease (LRTD) was defined according to the criteria used in the EBMT study on 'impact of COVID-19 on stem cell transplant recipients' and ECIL (European Conference on Infections in Leukemia) recommendations [2,19]. The resolution was defined as being alive with either clinical and/or virologic resolution of COVID-19.

3. Results

Eleven patients from 6 countries were enrolled in this study (6 males, 5 females). Patient and HSCT characteristics are summarized in Table 1. The median age of patients at COVID-19 diagnosis was 41 years (range 13–67; only one patient with age <18 years). Three patients received an allogeneic HSCT, and 8 autologous HSCT. The underlying disease were SSc (n = 5), MS (n = 3), Behçet's disease (n = 1), systemic juvenile idiopathic arthritis (Still's disease, n = 1), and neuromyelitis optica (n = 1), refractory to conventional treatments (n = 4 steroids; n = 2 cyclophosphamide; n = 2 mycophenolate mofetil; n = 1 colchicine; n = 1 rituximab). The patient, affected by an aggressive and highly refractory form of neuromyelitis optica, received an autologous and a subsequent allogeneic transplant procedure. At the time of SARS-CoV-2 infection, eight patients were in complete disease remission and 3 patients had signs of disease activity/progression. No GvHD signs/symptoms were present at infection onset.

Table 1
Characteristics of patients and HSCTs.

	Allogeneic (N = 3)	Autologous (N = 8)	Overall (N = 11)
Sex			
Male	1 (33.3%)	5 (62.5%)	6 (54.5%)
Female	2 (66.7%)	3 (37.5%)	5 (45.5%)
Age (years)			
Mean (SD)	24.7 (14.6)	47.1 (10.2)	41.0 (15.0)
Median [Min, Max]	20.0 [13.0, 41.0]	42.0 [39.0, 67.0]	41.0 [13.0, 67.0]
Comorbidities			
no	2 (66.7%)	4 (50.0%)	6 (54.5%)
yes	1 (33.3%)	4 (50.0%)	5 (45.5%)
Autoimmune disease			
Systemic sclerosis (diffuse subtype)	0 (0%)	5 (62.5%)	5 (45.5%)
Behçet's syndrome	1 (33.3%)	0 (0%)	1 (9.1%)
Juvenile idiopathic arthritis: Systemic (Stills)	1 (33.3%)	0 (0%)	1 (9.1%)
Multiple sclerosis	0 (0%)	3 (37.5%)	3 (27.3%)
Relapsing/remitting	0	1	1
Progressive	0	1	1
Aggressive	0	1	1
NMO	1 (33.3%)	0 (0%)	1 (9.1%)
Stem cell source			
BM	1 (33.3%)	0 (0%)	1 (9.1%)
PB	2 (66.7%)	8 (100%)	10 (90.9%)
Type of donor (allogeneic HSCT only)			
Identical sibling	1 (33.3%)		
Mismatched relative/ haploidentical	1 (33.3%)		
Unrelated	1 (33.3%)		
Time from HSCT to COVID-19 diagnosis (in days)			
Mean (SD)	1740 (2600)	1230 (1240)	1370 (1580)
Median [Min, Max]	318 [151, 4740]	733 [8.00, 3600]	422 [8.00, 4740]
Disease status at COVID19			
Complete remission	3 (100%)	5 (62.5%)	8 (72.7%)
Progression	0 (0%)	2 (25.0%)	2 (18.2%)
Active disease	0 (0%)	1 (12.5%)	1 (9.1%)
GvHD at COVID19 (allogeneic HSCT only)			
No	3 (100%)		
Other lung pathology			
No	3 (100%)	6 (75.0%)	9 (81.8%)
Yes (interstitial lung disease)	0 (0%)	2 (25.0%)	2 (18.2%)
Immunosuppressive drug(s) within 2 months prior to and after the COVID-19 episode			
No	3 (100%)	7 (87.5%)	10 (90.9%)
Yes	0 (0%)	1 (12.5%)	1 (9.1%)
COVID-19 vaccine received before infection			
No	1 (33.3%)	4 (50.0%)	5 (45.4%)
Yes	1 (33.3%)	2 (25.0%)	3 (27.3%)
Unknown	1 (33.3%)	2 (25.0%)	3 (27.3%)
Time from first vaccine to COVID-19 (in days)			
Median [Min, Max]	228	161.5 [40–283]	228 [40–283]

Abbreviations: BM, bone marrow; BOOP, bronchiolitis obliterans organizing pneumonia; COVID-19, coronavirus disease 2019; HSCT, hematopoietic stem cell transplant; max, maximum; min, minimum; NMO, Neuromyelitis Optica; PB, peripheral blood; SD, standard deviation.

3.1. Median time from transplant to COVID-19 diagnosis was 422 days (range 8–4740)

The following comorbidities were reported for this cohort: former smoker (n = 4), dyslipidemia (n = 2), high blood pressure (n = 1), pulmonary arterial hypertension (n = 1), diabetes (n = 1), interstitial lung disease (n = 2). Obesity was not reported. Baseline Karnofsky score was 100% in 4 cases, 90% in 3 cases, 80% in 1 case, 60% in 1 case and 50% in 1 case. At time of COVID-19 diagnosis, 4 patients were receiving low dose steroids (prednisone daily dose between 2 mg and 5 mg). In the previous 2 months, one patient received cyclophosphamide.

Clinical characteristics and outcomes of SARS-CoV-2 infection in this cohort are summarized in Table 2. All patients were symptomatic during the initial phase of SARS-CoV-2 infection. At diagnosis, 5 patients reported upper respiratory symptoms (i.e. rhinorrhea, sinusitis, otitis or pharyngitis), while 3 cases had cough, with sputum in one case. Overall, 6 patients had other symptoms: fever (n = 6), asthenia (n = 3), myalgia and/or arthralgia (n = 2), gastrointestinal symptoms (n = 2), loss of taste and smell (n = 2). At time of screening, no patients required supplemental oxygen therapy. All patients were PCR positive for SARS-CoV-2 on rhinopharyngeal swab, and diagnosed between March 2020 and May 2022. The SARS-CoV-2 variant B.1.1.529 (Omicron) was reported only in one case. Data on SARS-CoV-2 variants was not available for the other cases. Bronchoalveolar lavage (BAL) was obtained in one case, demonstrating a co-infection with *Streptococcus* spp. Another bacterial co-infection was observed in this cohort, due to *Moraxella catarrhalis*.

Table 2
Clinical characteristics and outcomes of SARS-CoV-2 infection.

	Allogeneic (N = 3)	Autologous (N = 8)	Overall (N = 11)
Year for COVID-19 diagnosis			
2020	1	3	4
2021	0	3	3
2022	2	2	4
Asymptomatic			
No	3 (100%)	8 (100%)	11 (100%)
Yes	0 (0%)	0 (0%)	0 (0%)
Upper respiratory symptoms			
No	1 (33.3%)	5 (62.5%)	6 (54.5%)
Yes	2 (66.7%)	3 (37.5%)	5 (45.5%)
At time of screening: oxygen requirement			
No	3 (100%)	8 (100%)	11 (100%)
COVID-19 treatment			
No	1 (33.3%)	6 (75.0%)	7 (63.6%)
Yes	2 (66.7%)	2 (25.0%)	4 (36.4%)
Hospitalization during COVID -19			
No (outpatient)	2 (66.7%)	3 (37.5%)	5 (45.5%)
Yes	1 (33.3%)	5 (62.5%)	6 (54.5%)
Intensive care unit admission			
No	3 (100%)	8 (100%)	11 (100%)
LRTD			
Possible	0 (0%)	2 (25.0%)	2 (18.2%)
Proven	1 (33.3%)	1 (12.5%)	2 (18.2%)
Use of ventilation			
No	3 (100%)	8 (100%)	11 (100%)
Last known COVID-19 status			
Alive, virologically and clinically resolved	3 (100%)	7 (87.5%)	10 (90.9%)
Alive, clinically resolved	0 (0%)	1 (12.5%)	1 (9.1%)
Last survival status			
alive	3 (100%)	8 (100%)	11 (100%)

Abbreviations: COVID-19, coronavirus disease 2019; LRTD, lower respiratory tract disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

At COVID-19 onset, 2 patients had neutrophil counts below 0.5 × 109/L, while one patient had lymphocyte counts below 0.5 × 109/L and 3 patients had lymphocyte counts between 0.5 and 1.0 × 109/L. All patients had platelet above 100 × 109/L. High value of C-reactive protein, equal to or greater than 10 mg/L, were observed in 5 cases. Immunoglobulin G levels were normal, equal to or greater than 6 g/L, in 4 cases (data missing in 7 patients).

Seven patients showed abnormal pulmonary radiological findings. These findings were non-specific in 3 cases. Four cases developed a lower respiratory tract disease (LRTD), possible (n = 2) or proven (n = 2).

Five patients were admitted to hospital at COVID-19 onset. Overall, hospitalization was required in 6 cases during the course of COVID-19, mainly related to the infection (n = 4). No patients required intensive care unit (ICU) care nor needed any ventilation support/supplemental oxygen.

Specific treatment was initiated in 4 patients, reflecting the knowledge at the time of COVID-19: remdesivir (n = 1), nirmatrelvir/ritonavir

(n = 1), sotrovimab (n = 1), immunoglobulins (n = 1). No additional steroid use was administered during the infection.

At the time of analysis, all patients are alive (100%). Median follow-up from COVID-19 diagnosis was 68 days (range 25–288). The follow-up was equal to or greater than 6 weeks from COVID-19 infection in 9/11 cases. All patients clinically resolved their SARS-CoV-2 infections. Ten patients had virologic and one patient had clinical resolution but was not retested with PCR.

Overall, 3 patients were vaccinated against SARS-Cov-2 with the BNT162b2 vaccine (Pfizer, BioNTech; 3 doses of vaccine in 2 patients, and 2 doses in 1 patient) after HSCT and developed the infection at a median time of 228 days (range 40–283 days) from the first dose vaccine. Data on vaccine-specific antibody or T cell responses before infection were not available.

4. Discussion

The new coronavirus SARS-CoV-2 caused unprecedented stress on health-care system including programs performing HSCT. Since 2020, the transplant community provided clear recommendations for the management of transplant recipients and their donors [20–22] through different stages of pandemic. A recent EBMT activity survey [23] described the pandemic challenge in providing patients access to HSCT treatment, showing for the first time in 31 years a drop in activity. Reductions have been more pronounced in non-malignant disorders, including ADs, since non-urgent transplants have been deferred according to interim EBMT guidelines from the start of the pandemic, mainly in 2020.

HSCT has evolved over the last 25 years as a specific treatment for patients with severe ADs, through eradication of the pathogenic immunologic memory and profound immune renewal and is recently facing a unique developmental phase across transplant centers [7]. During the pandemic, EBMT provided specific recommendations to properly guide the delivery of HSCT in this context, whilst maintaining quality and cautiously balancing risks and benefits against alternative non-transplant treatment options in each AD [24]. As reflection of EBMT guidelines provided during the pandemic, which advised HSCT activity deferral for AD indications [24], as well as disease-specific recommendations [25], the last EBMT survey reported an overall decrease of −45% for autologous HSCT procedures in ADs [23], most likely related to the SARS-CoV-2 pandemic within the predominant countries of activity in this field. Nevertheless, a total of 533 transplant procedures have been performed for ADs in this study period between March 2020 and May 2022. This strategy probably helped also to contain the number of infections, potentially explaining also the low numbers of COVID-19 cases reported in HSCT procedures performed for ADs, and mortality rates in AD population.

Currently, there is a gap of knowledge regarding COVID-19 course in HSCT recipients affected by ADs. In this analysis, 11 patients affected by ADs developed COVID-19 after HSCT procedure (n = 3 allogeneic transplant; n = 8 autologous transplant) with favorable outcomes. Overall, 4 cases developed LRTD and 6 cases required hospitalization, however, without necessity of ICU admission or ventilation/oxygen supply. All patients were regarded as having mild/moderate COVID-19 infection, and survival after infection was 100%.

Moreover, in patients without SARS-CoV-2 infection, this positive trend on survival has been confirmed by recent registry data, showing a stable non-relapse mortality (defined as death for whatever cause, without ever experiencing relapse) around 1% from 2015 through all the 2020, in MS patients treated with autologous HSCT [7].

Although we have information on used therapeutic interventions, the data do not allow detailed analysis of the potential effects of antiviral drugs or anti-inflammatory agents due to the small population and heterogeneity of interventions. Likewise, no conclusions can be drawn about the impact of the underlying AD and/or the intensity of transplant regiments on the outcomes of SARS-CoV2 infection.

Specific guidelines [24] and vaccination strategies have potentially contributed to minimize the risk of COVID-19 in AD population treated with HSCT [26]. Active immunization is essential to prevent SARS-CoV-2 infections in HSCT recipients [27,28], although the immune response to vaccines may be significantly impaired, mainly after B-cell depleting treatments [22]. In our cohort of patients, only 3 out of 11 had received a Covid-19 vaccination.

The low numbers reported in the EBMT study may be partially explained also by the end date of the data collection (May 2022) for this series, not accounting for the many Omicron cases that arose commonly in the population in the later parts of 2022. Overall, the favorable outcomes were surprising, as some patients had also reduced neutrophils and/or lymphocyte counts at the infection onset, transplant regimens used in autologous HSCT for ADs are generally more immunosuppressive than those used for other indications [7], and patients often receive other immunomodulatory treatments prior and after HSCT.

In conclusion, the observed favorable outcomes of COVID-19 in transplant recipients suggests that selected individuals with high risk of disease progression should not necessarily abandon HSCT as specific treatments. Although conducted within a small cohort, the current analysis describes a mild-moderate course of COVID-19 in transplant recipients affected by ADs, similar to the course observed in ADs under standard treatments. Although limited by small numbers, the outcome seems favorable as compared to the reported EBMT data on mortality in HSCT recipients transplanted for hematological malignancies but it should be acknowledged that the time-frames of infection were different and the outcome has improved over time. Vaccination strategies [18,29] and new treatments available for SARS-CoV-2 infection [18,22,30], may be useful to further minimize the infectious risk in AD population receiving HSCT. Additional beneficial effects may come from the widespread vaccination program within the general population and its potential protection also for frail patients, including ADs and HSCT recipients [27,28].

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Author statements

RG, JS, RdeC, PL led on concept and design, provided expert and analytical feedback, and worked as a writing committee. NSK and GT managed the registry data. All others provided data and critically reviewed first a preliminary and then the final version of the manuscript.

Declaration of competing interest

All authors have no competing interests directly related to this manuscript.

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