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RESEARCH ARTICLE

Common points of therapeutic intervention in COVID-19 and in allogeneic hematopoietic stem cell transplantation associated severe cytokine release syndrome

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ABSTRACT

Allogeneic hematopoietic stem cell transplantation (HSCT) and coronavirus disease 2019 (COVID-19) infection can both lead to severe cytokine release syndrome (sCRS) resulting in critical illness and death. In this single institution, preliminary comparative case-series study we compared clinical and laboratory covariates as well as response to tocilizumab (TCZ)-based therapy of 15 allogeneic-HSCT- and 17 COVID-19-associated sCRS patients. Reaction to a TCZ plus posttransplant cyclophosphamide (PTCY) consolidation therapy in the allogeneic-HSCT-associated sCRS group yielded significantly inferior long-term outcome as compared to TCZ-based therapy in the COVID-19-associated group ($P = 0.003$). We report that a TCZ followed by consolidation therapy with a Janus kinase/signal transducer and activator of transcription (JAK/STAT) inhibitor given to 4 out of 8 critically ill COVID-19 patients resulted in their complete recovery. Non-selective JAK/STAT inhibitors influencing the action of several cytokines exhibit a broader effect than TCZ alone in calming down sCRS. Serum levels of cytokines and chemokines show similar changes in allogeneic-HSCT- and COVID-19-associated sCRS with marked elevation of interleukin-6 (IL-6), regulated upon activation normal T-cell expressed and secreted (RANTES), monocyte chemoattractant protein-1 (MCP-1) and interferon γ-induced protein 10 kDa (IP-10) levels. In addition, levels of IL-5, IL-10, IL-15 were also elevated in allogeneic-HSCT-associated sCRS. Our multi-cytokine expression data indicate that the pathophysiology of allogeneic-HSCT and COVID-19-associated sCRS are similar therefore the same clinical grading system and TCZ-based treatment approaches can be applied. TCZ with JAK/STAT inhibitor consolidation therapy might be highly effective in COVID-19 sCRS patients.

KEYWORDS

COVID-19, allogeneic-HSCT, severe CRS therapy, CAR-T-cell, multi-cytokine levels

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INTRODUCTION

With the increasing use of haploidentical grafts cytokine release syndrome (CRS) has become a more often seen complication in the field of hematology and allogeneic hematopoietic stem

cell transplantation (HSCT) practice. Indeed, as the Hungarian National Center for Hematology and Infectious Disease, over the past decade we have gathered extensive experience with the diagnosis and treatment of CRS. Annually, we encounter an average of 40–50 cases most of them developing as a complication of haploidentical HSCT or serious infections.

Clinical experiences have been gathered from a large number of patients receiving bispecific/trispecific killer cell engager (BIKE/TRIKE) and chimeric antigen receptor-T-cell (CAR-T-cell) therapies or undergoing haploidentical allogeneic-HSCT followed by posttransplant cyclophosphamide (PTCY) for graft versus host disease (GVHD) prevention [1–5]. Accumulating scientific evidence supports the idea that CRS and other allogeneic-HSCT related complications such as rejection, secondary hemophagocytic lympho-histiocytosis/macrophage activation syndrome (sHLH/MASs), veno-occlusive liver disease (VOD), acute GVHD, hyper-engraftment syndrome and immune-reconstitution syndrome with central nervous system (CNS) dysfunction should be regarded as different presentations of the same multisystemic hyperinflammatory syndrome [6, our unpublished observations]. Eventually, characteristics, composition and dynamics of the multi-cytokine „cloud pattern" will determine the developing clinical picture.

In 2014, *Lee* et al. were the pioneers to describe and classify CRS and they also published the first therapeutic recommendations [7]. The incidence rate of allogeneic-HSCT related severe CRS (sCRS) is 7–17% in different publications and is associated with a very poor prognosis. Sadly enough, our therapeutic experience and knowledge is still limited [1–3]. More recently, CAR-T cell therapies have provided information on the clinical picture, severity stratification and management of CRS but outside the IL-6 pathway inhibition no relevant studies have been conducted on the complex therapy of this serious complication. Later on, tocilizumab (TCZ) treatment for CAR-T-cell therapy induced sCRS was approved by the Food and Drug Administration (FDA) [8].

In allogeneic-HSCT related sCRS TCZ is used as a bridging agent in the critical 48–72-hour post-transplant period and subsequent PTCY is applied to attenuate sCRS in the vast majority of cases. In case of sCRS this two-step consolidation treatment is required to achieve a complete cure of CRS.

Severe CRS is also a major cause of coronavirus disease-2019 (COVID-19) associated morbidity and mortality [9]. Based on our extensive experience with allogeneic HSCT and infectious disease we were among the first in the world to use TCZ treatment of COVID-19 associated sCRS patients. The previously published 9 randomized clinical trials (RCT) and 23 retrospective studies on the use of TCZ in severe and/or critical COVID-19 [10] yielded controversial results. The decisive result was provided only recently by the REVOVERY trial which provided unequivocal evidence on the positive effect of TCZ on mortality [11]. On 24 June 2021, the FDA issued an emergency use authorization (EUA) for TCZ treatment to patients with severe or critical COVID-19 who received systemic corticosteroids [12]. Subsequently, on 16 August 2021, the European Medicines Agency (EMA) began to assess TCZ treatment in the same indication [13]. International data and our own experience suggest, however, that TCZ monotherapy may not always be sufficient for the treatment of COVID-19 associated sCRS [14].

In our work we postulated that the serum multi-cytokine expression pattern might play a similar role in both allogeneic-HSCT and COVID-19 related sCRS and there may be common druggable underlying pathways in their pathophysiology. Several cytokines and chemokines that play a role in the development of sCRS share the Janus kinase inhibitor/signal transducer and activator of transcription (JAK/STAT) second messenger pathway [5, 15–17]. Based on this, we hypothesized that subsequent to the administration of TCZ non-selective JAK/STAT inhibitors might substantially improve the therapeutic results of seriously ill COVID-19 infected patients [15, 17]. To successfully treat COVID-19-associated sCRS we adopted the philosophy of two-step immunosuppression from our allogeneic HSCT practice. Furthermore, based on the available literature, we compared the clinical, laboratory, multi-cytokine patterns and treatment outcomes of 3 clinical sCRS presentations (CAR-T-cell vs COVID-19 vs allogeneic-HSCT) of different etiology.

MATERIALS AND METHODS

Ethical considerations

Retrospective workup of data from allogeneic-HSCT patients has been approved by our Institutional Ethical Review Board. With regard to prospective data collection and analysis all patients (or their responsible family members) signed a proper informed consent form. Prior to allogeneic-HSCT patients signed an informed consent regarding the collection of their medical data for the European Blood and Marrow Transplantation/International Blood and Marrow Transplantation Registry (EBMT/IBMTR) and utilization of their medical data for scientific purposes. Treatment of COVID-19 patients was carried out in the framework of the CONTRAST (**CO**mparing **N**ovel **TR**eatment Strategies **A**gainst **S**ARS-CoV-**T**wo) clinical trial initiated by our hospital. The trial was approved by the Scientific and Research Ethics Committee of the Hungarian National Medical Scientific Council (ETT-TUKEB IV/3937-1/2020/EKU) [18, 19].

Patient stratification

Based primarily on the severity of COVID-19-associated CRS, patients were allocated into 4 groups (Table S1.): severe (1), critical (2), presence of risk factor(s) and/or laboratory data predicting severe CRS (3), and secondary hemophagocytic lympho-histiocytosis/macrophage activation syndrome (sHLH/MAS) (4). In the CONTRAST trial formerly published criteria for patient selection have been used

[9, 18–22]. With regard to CRS grading, criteria published by *Lee* et al. were followed since their introduction into the practice [7]. The application of an upgraded version of the *Lee/Santomasso* classification or a similar system did not influence the allocation of patients [23, 24].

Measurements of IL-6 and multi-cytokine levels

For routine monitoring of serum IL-6 levels the Advia Centaur IL-6 (Siemens, Ireland, Dublin) one step chemiluminescent assay was applied (normal value: 2.2–4.4 pg/mL). For measuring serum levels of 20 different cytokines (interferon α2, (IFNα2), IFNγ, interleukin-1α (IL-1α), IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL-15, IL-17A, regulated upon activation, normal T-cell expressed and secreted (RANTES), monocyte chemoattractant protein-1 (MCP-1), interferon γ-induced protein 10 kDa (IP-10), macrophage-inflammatory protein-1α (MIP-1α), tumor necrosis factor α (TNFα), and TNFβ HCYTA-60K Millipore MILLIPLEX MAP-Human Cytokine/Chemokine/Growth Factor Panel A - Immunology Multiplex Assay (Merck KgaA, Darmstadt, Germany) was used.

Statistical analysis

GraphPad Prism 6 for Windows (version 6.01) was used for all statistical analyses. All quantitative data are expressed as the mean ± standard deviation (95% CIs). Mean values of the different groups were compared using a two-tailed unpaired *t*-test. Welsh's correction was used if variances were unequal (asterixes). Fisher's exact test was performed to compare proportions of gender, co-morbidity, symptoms, grade, therapy and clinical outcome. $P<0.05$ indicates the difference is statistically significant.

RESULTS

Patient characteristics

In the present study two groups of sCRS patients with completely different etiology were compared. The first group consisted of 15 cases out of 294 patients who underwent allogeneic-HSCT between April 1, 2017, and June 20, 2020 and fulfilled inclusion criteria. Into the second group 17 COVID-19-associated cases were enrolled and classified out of 408 individuals treated in the Department of Infectious Diseases and the Intensive Care Unit (ICU) of the institution between March 20, 2020 and June 20, 2020. This time period corresponds to the first wave of the coronavirus pandemic affecting Hungary. Serum levels of 20 cytokines were measured in the sera of 14/17 COVID-19 and 4 allogeneic-HSCT-associated cases. All patients received tocilizumab-based anti-cytokine treatment in both groups. Age was significantly higher in the COVID-19 sCRS group (P = 0.004). Gender distribution was not different for both groups. Among patient co-morbidities coronary heart disease (CHD) +/- atherosclerosis was significantly higher in the COVID-19 sCRS cohort (P = 0.04). Incidence of hypertension also was higher in the COVID-19 sCRS group (65% vs 33%) but the difference was not significant (Table 1). In the allogeneic-HSCT related sCRS group pre-transplant underlying diseases were mainly myeloid neoplasms (73%). A positive lung auscultation on physical examination occurred more frequently in COVID-19 sCRS group (82% vs 60%).

Laboratory findings

Figure 1 and Fig. S1. shows IL-6, CRP, D-dimer and ferritin results for both groups before and sequentially after the application of TCZ. Prior to administration of TCZ (day 0) IL-6 levels were 80–100 times of the normal value in both groups, being higher in the COVID-19 group (P = 0.71). Values peaked on day 3 in the allogeneic-HSCT group and on day 5 in the COVID-19 cohort. The difference became significant by day 7, IL-6 being higher in the COVID-19 group (P = 0.01). In both groups CRP peaked on the first post-TCZ day (day 1) but this finding was not significant. In the COVID-19 group CRP returned to normal by day 10, whereas in the allogeneic-HSCT cohort it showed a gradual decline, but its value remained fluctuating at higher levels for a longer period. We observed a marked difference in the time course of D-dimer measurements. Compared to the allogeneic-HSCT group extremely high levels of D-dimer were detected in the COVID-19 group on day 0 (P = 0.12) and values remained elevated for more than two weeks also in the post-treatment period. In the allogeneic-HSCT cohort D-dimer reached the highest level on day 1 and showed a gradual decrease over time. On day 0, serum ferritin was higher in the allogeneic-HSCT group (P = 0.13). Values peaked on day 3 in the allogeneic-HSCT group and on day 5 in the COVID-19 cohort. Ferritin levels tended to remain high in the allogeneic-HSCT group and the difference between cohorts reached significance on days 7, 10 and 15 (P < 0.001, P = 0.02, P = 0.01).

Multi-cytokine pattern in COVID-19 vs allogeneic-HSCT associated sCRS

The evolution of multi-cytokine levels in both sCRS groups is illustrated by Fig. 2. Further detailed results are shown in Table S2. For statistical analysis of the multi-cytokine pattern samples of COVID-19- and allogeneic-HSCT-associated sCRS patients were allocated into two groups. The first group contained samples taken on days 0–3 of TCZ administration (13 vs 12 samples), whereas the second contained samples taken on days 5–8 following TCZ treatment (7 vs 7 samples).

Constantly low values of IFNα2, IL-1α, IL-1β, IL-2, IL-12, IL-17A were observed in both groups. Among the 20 cytokines/chemokines measured on 0–3 days after TCZ administration elevated IFNγ, IL-6, IL-8, IP-10, MCP-1 and RANTES patterns were detected in the COVID-19 sCRS group. An even more widespread cytokine activation was found in the allogeneic-HSCT sCRS group, including IFNγ, IL-5, IL-6, IL-8, IL-10, IL-15, IP-10, MCP-1, RANTES, MIP-1α and TNFα. On days 0–3 post-TCZ administration, IL5

Table 1. Main clinical characteristics of COVID-19- and allogeneic-HSCT-associated sCRS

	COVID-19 (n = 17)	Allogeneic-HSCT (n = 15)	P value
Characteristic			
Age (IQR), y	63.41 ± 5.05 (40–78)	49.93 ± 6.56 (27–68)	0.004
Gender, n (%)			
Male	11/17 (65%)	8/15 (53%)	0.72
Female	6/17 (35%)	7/15 (47%)	
Diagnosis of hematological malignancies, n (%)			
Acute myeloid leukemia	NA	8/15 (53%)	NA
Acute lymphoid leukemia	NA	2/15 (13%)	NA
Myeloproliferative neoplasm	NA	3/15 (20%)	NA
Lymphoproliferative neoplasm	NA	2/15 (13%)	NA
Co-morbidity, n (%)			
Hypertension	11/17 (65%)	5/15 (33%)	0.16
Type 2 diabetes	4/17 (24%)	5/15 (33%)	0.70
CHD+/- atherosclerosis	7/17 (42%)	1/15 (7%)	0.04
CRF or acute renal failure	2/17 (12%)	1/15 (7%)	>0.99
COPD	3/17 (18%)	2/15 (13%)	>0.99
Multiple myeloma	1/17 (6%)	0/15 (0%)	>0.99
Metastatic breast cancer	2/17 (12%)	1/15 (7%)	>0.99
ACEI/ARB treatment, n (%)	8/17 (47%)	6/15 (40%)	0.73
Disease status, n (%)			
Complete remission	NA	11/15 (73%)	NA
Active disease/Stabile disease	NA	4/15 (27%)	NA
Conditioning regimen, n (%)			
MAC	NA	8/15 (53%)	NA
RIC/NMA	NA	7/15 (47%)	NA
Donor, n (%)			
Haploidentical	NA	9/15 (60%)	NA
Unrelated	NA	4/15 (27%)	NA
Matched related sibling	NA	2/15 (13%)	NA
Stem cell source PBSC, n (%)	NA	15/15 (100%)	NA
Physical examination, n (%)			
Positive lung auscultation on physical examination (evidence of rales/ crackles)	14/17 (82%)	9/15 (60%)	0.24
Images, n (%)			
Chest X-rays: bilateral infiltrates	7/9 (78%)	ND	NA
Chest CT scan: bilateral subpleural infiltrates with GGO	13/13 (100%)	ND	NA

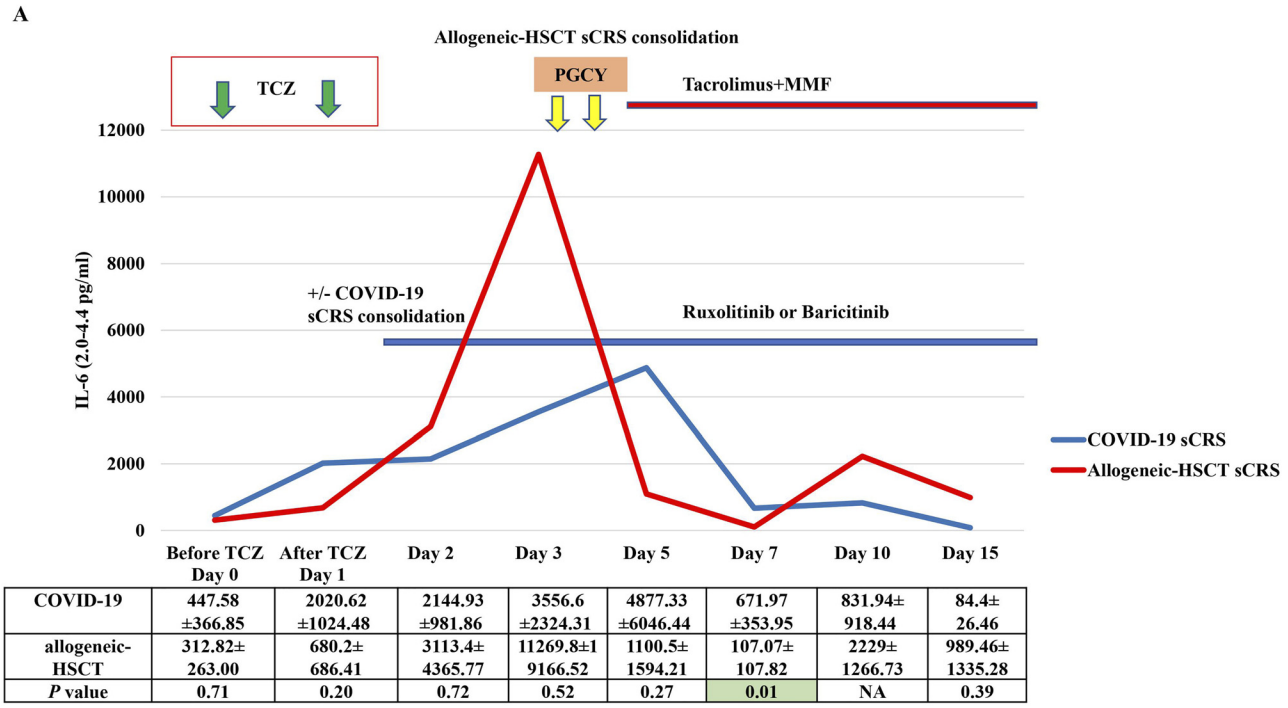
Abbreviations: HSCT: hematopoietic stem cell transplantation; sCRS: severe cytokine release syndrome; IQR: interquartile range; CHD: coronary heart disease; CRF: chronic renal failure; COPD: chronic obstructive pulmonary disease; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ND: not done; NA: not applicable or not enough data; MAC: myeloablative conditioning; RIC: reduced intensity conditioning; NMA: nonmyeloablative conditioning; PBSC: peripheral blood stem cells, CT: computer tomography; GGO: ground-glass opacity.

Note: Data are all patients % or means ±SD, confidence level 95%, $1960s_{x\sigma,}$ significant different $P < 0.05$.

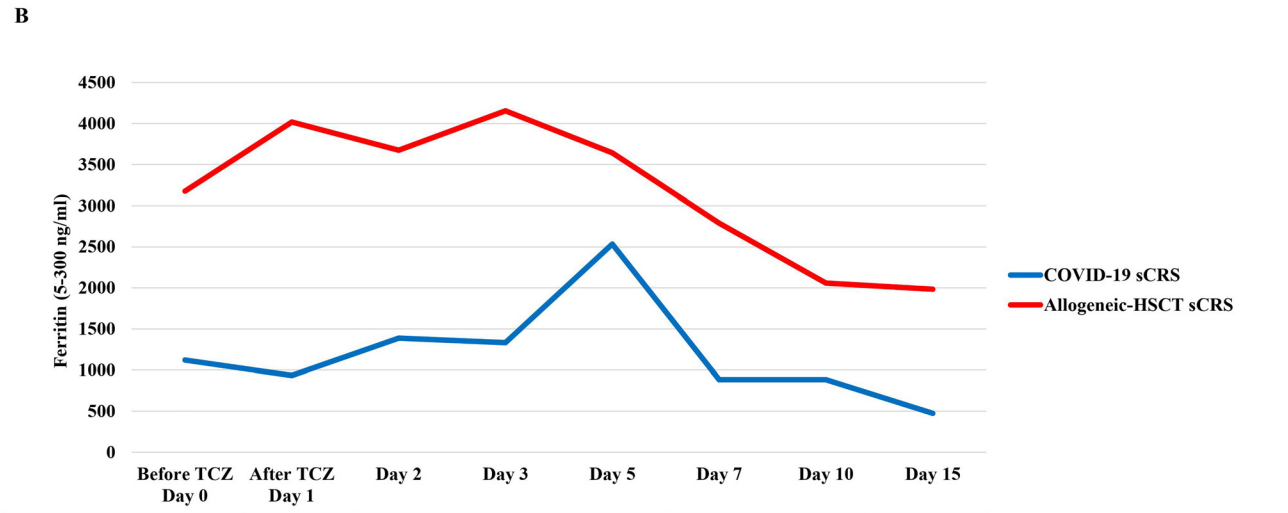
($P = 0.04$) and IL-15 ($P < 0.001$) were significantly increased in the allogeneic-HSCT sCRS group and RANTES ($P = 0.005$) was significantly elevated in the COVID-19 sCRS group. Among cytokines with normal or decreased levels, MIP-1α (P=0.010) in the allogeneic-HSCT sCRS group and IL-4 ($P = 0.02$), IL-13 ($P = 0.01$), and TNFβ ($P = 0.02$) in the COVID-19 sCRS group showed a significant difference. On days 5–8 after TCZ treatment, attenuation of increased cytokine levels was observed in both groups. Within this time frame the IL-15 level remained significantly different in allogeneic-HSCT sCRS ($P = 0.001$) similar to RANTES ($P = 0.03$), IL4 ($P = 0.01$), and IL-13 ($P = 0.01$) in COVID-19 sCRS patients. A significant rise of MCP-1 ($P = 0.008$) on days 5–8 was seen in allogeneic-HSCT sCRS patients. In addition, IL-8 and IL-10 levels were higher in both intervals in the allogeneic-HSCT cohort, also without significant differences.

Clinical symptoms and classification of CRS

For diagnosis and grading of CRS we used the stratification developed for adoptive T-cell therapies (CAR-T-cell) [7]. Severe CRS was observed in 15 allogeneic-HSCT patients of whom 3 were Grade 2 with comorbidity, 8 Grade 3, and 4 Grade 4 (1 progressed to sHLH). For GVHD prevention 14 patients received PTCY consolidation and one received an in



	Before TCZ Day 0	After TCZ Day 1	Day 2	Day 3	Day 5	Day 7	Day 10	Day 15
COVID-19	447.58 ±366.85	2020.62 ±1024.48	2144.93 ±981.86	3556.6 ±2324.31	4877.33 ±6046.44	671.97 ±353.95	831.94± 918.44	84.4± 26.46
allogeneic-HSCT	312.82± 263.00	680.2± 686.41	3113.4± 4365.77	11269.8±1 9166.52	1100.5± 1594.21	107.07± 107.82	2229± 1266.73	989.46± 1335.28
P value	0.71	0.20	0.72	0.52	0.27	0.01	NA	0.39



	Before TCZ Day 0	After TCZ Day 1	Day 2	Day 3	Day 5	Day 7	Day 10	Day 15
COVID-19	1120.07 ± 570.86	933.5 ± 243.11	1387.85 ± 657.83	1332.6± 592.5	2533.4 ± 2674.1	883.69 ± 427.32	883.83 ± 336.86	475 ± 158.42
allogeneic-HSCT	3176.33± 2213.19	4019.28± 2475.14	3675.44± 2168.17	4154.33± 2483.68	3642.62± 1581.13	2790.2± 712.75	2059.33± 1107.42	1983± 651.01
P-value	0.13	0.06	0.09	0.07	0.51	<0.001	0.02	0.01

Fig. 1. Changes of relevant laboratory values of COVID-19 and allogeneic-HSCT patients with sCRS before and sequentially after tocilizumab treatment. Comparisons of IL-6 (A) and ferritin (B) levels in COVID-19 and allogeneic-HSCT associated sCRS. After two doses of tocilizumab obviously need for consolidation treatment. For allogeneic-HSCT sCRS the administration of PTCY+tacrolimus+MMF provides effective sCRS disease control. For COVID-19 sCRS after tocilizumab treatment, the administration of consolidation with JAK/STAT inhibitor might provide effective control of sCRS.

Abbreviations: HSCT: hematopoietic stem cell transplantation; sCRS: severe cytokine release syndrome; PTCY: posttransplant cyclophosphamide; MMF: mycofenolate-mofetil; NA: not applicable or no enough data. Note: Data are means ±SD, confidence level 95%, $1960s_{x\sigma}$, significant different $P < 0.05$

vitro TCR$\alpha\beta$-depleted graft (Fig. S2). Of the 17 COVID-19 sCRS patients 5 were Grade 2 with comorbidity, 4 were Grade 3, and 8 were Grade 4 (1 patient progressed to sHLH). The incidence of grade 4 CRS was higher in the COVID-19 group, but the difference was statistically not significant (47% vs 27%, $P = 0.29$). Clinical symptoms and classification for both groups is summarized in Fig. S2. With regard to sCRS associated symptoms, hypotension and capillary-leak syndrome had meaningful differences between the two groups. Hypotension incidences were 87% in allogeneic-

A

Cytokine Normal value (pg/ml)	0-3 days after tocilizumab mean ±SD (range IQR) COVID-19 sCRS (N=13)	Allogeneic-HSCT sCRS (N=12)	P value
IFNγ (22-45)			0.26
IL-5 (21-44)			**0.04**
IL-6 (20-42)			0.75
IL-8 (21-44)			0.10
IL-10 (87-181)			0.22
IL-15 (104-216)			**<0.001**
IP-10/ CXCL10 (67-139)			0.27
MCP-1/ CCL2 (101-210)			0.10
RANTES/CCL-5 (40-84)			**0.005**
MIP-1α/CCL3 (74-153)			**0.010**
TNFα (123-256)			0.074
IFNα2 (208-432)			0.10
IL-1α (140-291)			0.35
IL-1β (45-94)			0.38
IL-2 (18-38)			0.08
IL-4 (19-40)			**0.02**
IL-12 (p70) (103-214)			0.80
IL-13 (197-409)			**0.01**
IL-17A (40-82)			0.43
TNFβ (53-111)			**0.02**

B

Cytokine Normal value (pg/ml)	5-8 days after tocilizumab mean ±SD (IQR) COVID-19 sCRS (N=7)	Allogeneic-HSCT sCRS (N=7)	P value
IFNγ (22-45)			0.32
IL-5 (21-44)			0.92
IL-6 (20-42)			0.67
IL-8 (21-44)			0.28
IL-10 (87-181)			0.43
IL-15 (104-216)			**0.001**
IP-10/ CXCL10 (67-139)			0.20
MCP-1/ CCL2 (101-210)			**0.008**
RANTES/CCL-5 (40-84)			**0.03**
MIP-1α/CCL3 (74-153)			0.47
TNFα (123-256)			0.57
IFNα2 (208-432)			0.28
IL-1α (140-291)			0.32
IL-1β (45-94)			0.16
IL-2 (18-38)			0.93
IL-4 (19-40)			**0.01**
IL-12 (p70) (103-214)			0.65
IL-13 (197-409)			**0.01**
IL-17A (40-82)			0.21
TNFβ (53-111)			0.12

Cytokine levels colour scales: Decreased value; Normal value; >1-<10x upper normal value; >10-<100x upper normal value; >100x upper normal value

Fig. 2. Comparisons of cytokine level changes after tocilizumab-based therapy in COVID-19 and allogeneic-HSCT-associated sCRS. (A) Cytokine level changes 0–3 days after tocilizumab-based therapy. (B) Cytokine level changes 5–8 days after tocilizumab-based therapy. Color coding: yellow background, decreased value; blue background, normal value; pink background, >1-<10x upper normal value; purple background, >10-<100x upper normal value; red background, >100x upper normal value; green background: significant different Abbreviation: HSCT: hematopoietic stem cell transplantation; sCRS: severe cytokine release syndrome; IQR: interquartile range (IQR); N: cytokine sample number; IFN: interferon; IL: interleukin; TNF: tumor necrosis factor; IP-10/CXCL10: interferon γ-induced protein 10 kDa/C-X-C motif chemokine 10; MCP-1-/CCL2: monocyte chemoattractant protein-1/C-C motif chemokine ligand 2; RANTES/CCL-5: regulated upon activation, normal T cell expressed and secreted/C-C motif chemokine ligand 5; MIP-1α-CCL3: macrophage inflammatory protein-1α/C-C motif chemokine ligand 3. Note: Data are all patients % or means ±SD, confidence level 95%, $1960s_{x\sigma}$, significant different $P < 0.05$ (green background).

Table 2. Treatment characteristics in patients with severe CRS

	COVID-19 (n = 17)	Allogeneic-HSCT (n = 15)	P value
Characteristic			
Onset of CRS: Time to accelerated phase of illness for COVID-19 or time after allograft infusion (IQR), d (range)	8.31 ± 1.55 (5–14)	1.20 ± 0.37 (0–3)	<0.001
Antiviral therapy for COVID-19, n (%)			
Azithromycin	12/17 (71%)	NA	NA
Hydroxychloroquine	7/17 (41%)	NA	NA
Chloroquine	2/17 (12%)	NA	NA
Favipiravir	7/17 (41%)	NA	NA
Oseltamivir	2/17 (12%)	NA	NA
Treatment approach for sCRS, n (%)			
Oxygen therapy			
Nasal cannula	5/17 (29%)	5/15 (33%)	>0.99
Mechanical ventilation	7/17 (42%)	3/15 (20%)	0.27
Time of mechanical ventilation (IQR), d	18.71 ± 8.93 (6–46)	7.66 ± 9.11 (1–19)	0.23
Mask oxygen or high flow oxygen	5/17 (29%)	7/15 (47%)	0.47
Tocilizumab administration	17/17 (100%)	15/15 (100%)	>0.99
Day of tocilizumab administration following the commencement of COVID-19 and HSCT-associated sCRS (IQR), d (range)	1.47 ± 0.56 (0–4)	1.53 ± 0.58 (0–3)	0.94
Dose schedule of tocilizumab, n (%)			
TCZ 1x8 mg/kg	-	13/15 (86%)	NA
TCZ 2x8 mg/kg	16/17 (94%)	1/15 (7%)	NA
TCZ 3x8 mg/kg	1/17 (6%)	1/15 (7%)	NA
Methylprednisolone, n (%)	5/17 (29%)	6/15 (40%)	0.71
„Consolidation treatment", n (%)	4/17 (24%)	14/15 (93%)[a]	<0.001
GVHD prevention with PTCY+tacrolimus+MMF, n (%)	NA	14/15 (93%)	NA
JAK/STAT inhibitor, n (%)	4/17 (24%)	0	NA
Ruxolitinib	2/17 (12%)	0	NA
Baricitinib	2/17 (12%)	0	NA

Abbreviations: HSCT: hematopoietic stem cell transplantation; sCRS: severe cytokine release syndrome; IQR: interquartile range; ND: not done; NA: not applicable or not enough data; TCZ: tocilizumab; GVHD: graft versus host disease; PTCY: posttransplant cyclophosphamide; MMF: mycofenolate-mofetil; JAK/STAT: Janus kinase-signal transducer and activator of transcription.

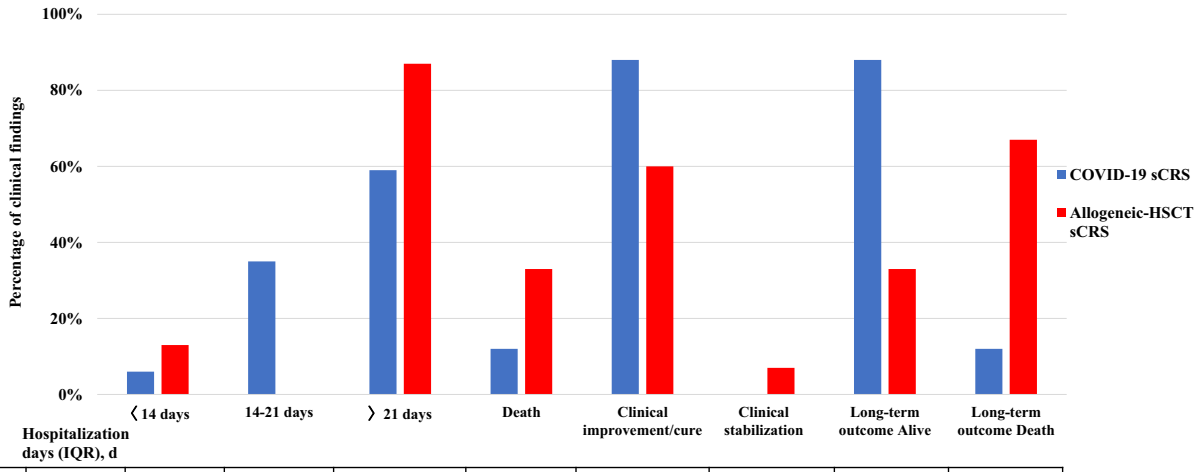
Note: Data are all patients % or means ±SD, confidence level 95%, $1960s_{x\sigma}$, significant different $P < 0.05$.

[a]1 patient received 2. allogeneic HSCT with in vitro TCR$\alpha\beta$+CD19 depleted graft.

HSCT and 42% in COVID-19 (P = 0.036). Capillary-leak syndrome was also significantly higher in the allogeneic-HSCT sCRS group (87% vs 0%, $P < 0.001$). Progression to respiratory failure and a need for intensive care and mechanical ventilation was more often observed in COVID-19 patients (47 vs 33%, P = 0.4905, and 42 vs 20%, P = 0.2654).

Therapeutic characteristics, treatment results and long-term outcome

The allogeneic-HSCT patient cohort developed sCRS after a median of 1.20 ± 0.37 days, significantly earlier than that observed in the COVID-19 sCRS group (8.31 ± 1.55 days, $P < 0.001$). Treatment characteristics, results and long-term outcomes are illustrated in Table 2 and Fig. 3. The need for oxygen therapy did not differ. All patients in both groups received TCZ treatment. Following diagnosis of sCRS TCZ therapy was initiated in the early stage of the pathologic process at almost identical time point in both cohorts (at days 1.53 ± 0.58 vs 1.47 ± 0.56). A difference was seen, however, in TCZ doses required for recovery. The dose of TCZ was 8 mg/kg in all patients. In the allogeneic-HSCT sCRS group, 86% of patients received only 1 dose TCZ, unlike in the COVID-19 sCRS group where 94% of cases received 2 doses. Corticosteroid use did not differ between allogeneic-HSCT and COVID-19 sCRS cohort. Post-TCZ consolidation therapy was significantly more often used in the allogeneic-HSCT sCRS group (93% vs 24%, $P < 0.001$). It is very important, however, that the type of consolidation treatment was entirely different between the two groups: PTCY+tacrolimus+ mycofenolate-mofetil (MMF) for allogeneic-HSCT and JAK/STAT inhibitor (ruxolitinib or baricitinib) in COVID-19 sCRS patients. We emphasize that 4 critical COVID-19 patients with sCRS were cured using a combined treatment with the TCZ+JAK/STAT inhibitor. Length of hospital stay was significantly longer in the allogeneic-HSCT group (37.46 ± 12.23 vs 25.29 ± 4.94



COVID-19 sCRS	25.29±4.94 (6-46)	1/17 (6%)	6/17 (35%)	10/17 (59%)	2/17 (12%)	15/17 (88%)	0/17 (0%)	15/17 (88%)	2/17 (12%)
Allogeneic-HSCT sCRS	37.46±12.23 (9-115)	2/15 (13%)	0	13/15 (87%)	5/15 (33%)	9/15 (60%)	1/15 (7%)	5/15 (33%)	10/15 (67%)
P value	0.04	0.59	0.02	0.12	0.21	0.11	0.47	0.003	0.003

Fig. 3. Hospitalization time and short-term and long-term outcomes of patients in both groups with sCRS in COVID-19 group and Allogeneic-HSCT group

Abbreviations: HSCT: hematopoietic stem cell transplantation; sCRS: severe cytokine release syndrome; IQR: interquartile range; NA: not applicable or no enough data.

Note: Data are means ±SD, confidence level 95%, $1960s_{x\sigma}$, significant different $P < 0.05$.

days, $P = 0.04$). No difference could be detected regarding the short-term outcome (Table S3). However, the long-term outcome proved to be significantly worse for allogeneic-HSCT sCRS compared to COVID-19 sCRS (33% vs 88%, $P = 0.003$).

DISCUSSION

Severe CRS is a spectrum of multisystemic hyper-inflammatory syndromes being sHLH/MAS the most serious and life-threatening manifestation [9, 25, 26]. Our experience and results indicate that clinical grading stratifications developed by *Lee* et al. for CAR-T cell-associated CRS [7, 24] and the HLH scoring system by *Fardet* et al. [22] can be readily applied for allogeneic-HCT and COVID-19 associated sCRS [15, 16, 23]. We successfully utilized these scoring systems in our practice and recommend its use also for other investigators. In addition, we propose that a two-step combined consolidation therapeutic approach is justified for the treatment of both sCRS types. Typically, COVID-19-associated sCRS starts with a sudden and rapid deterioration in the general condition and a quick increase in the oxygen requirement of patients usually 7–10 days after the appearance of the first symptoms. The short and quick progression – sometimes lasting only for a few hours – is the time when hyperinflammation turns multisystemic. Acute respiratory distress syndrome (ARDS) and multi-organ involvement develops quickly and high angiotensin converting enzyme receptor 2 (ACE2) expressing organs are specially jeopardized [27]. The presence of circulating viral RNA is closely associated with the commencement of CRS and it is an indicator of poor prognosis [28].

The evolution of pathophysiological processes in COVID-19 and allogeneic-HSCT sCRS is illustrated in Fig. 4. In COVID-19 infection the pathologic flow of events is initiated by the innate immune system and is followed by an IFNγ-boosting Th1 cell response similar to that observed in bats [29]. As a subsequent step Th1 cell response subsides and IL-6 triggers a Th17 cell response. At the same time a decrease in the proportion of Th2 cell and Treg cell populations develops. As a result of the skewed Th17 cell response, IL-17A quickly attracts inflammatory cells, such as neutrophil granulocytes and monocytes/macrophages to the lungs, leading to severe inflammation, tissue damage and degradation [30–32]. Pathological lesions of the lungs are further worsened by the pro-inflammatory properties of type-2 alveolar cells. High levels of IL-6 and other multi-cytokine production lead to respiratory, cardiac, endothelial, renal, hepatic and central nervous system (CNS) dysfunction with predominant lung involvement. COVID-19 CRS is late-onset as CRS that develops between the 5th and 14th days after infection. For the present series of patients this occurred on day 8.31 ± 1.55.

In the haploidentical allogeneic HSCT setting the encounter of the immune systems of the donor and the recipient may lead to the development of a fulminant cytokine storm. In this case severe CRS can develop within 12–24 h after donor grafting and is influenced by donor and recipient risk factors [2, 4, 5]. Therefore, the allogeneic-HSCT associated sCRS is called immediate-onset sCRS. Our patient population developed sCRS on days 1.20 ± 0.37 which is significantly shorter than that in COVID-19 sCRS ($P < 0.001$).

We followed alterations of laboratory tests shortly after CRS started to develop and sequentially after the administration of TCZ in both sCRS groups. Changes of IL-6, CRP and D-dimer in allogeneic-HSCT- and COVID-19 sCRS

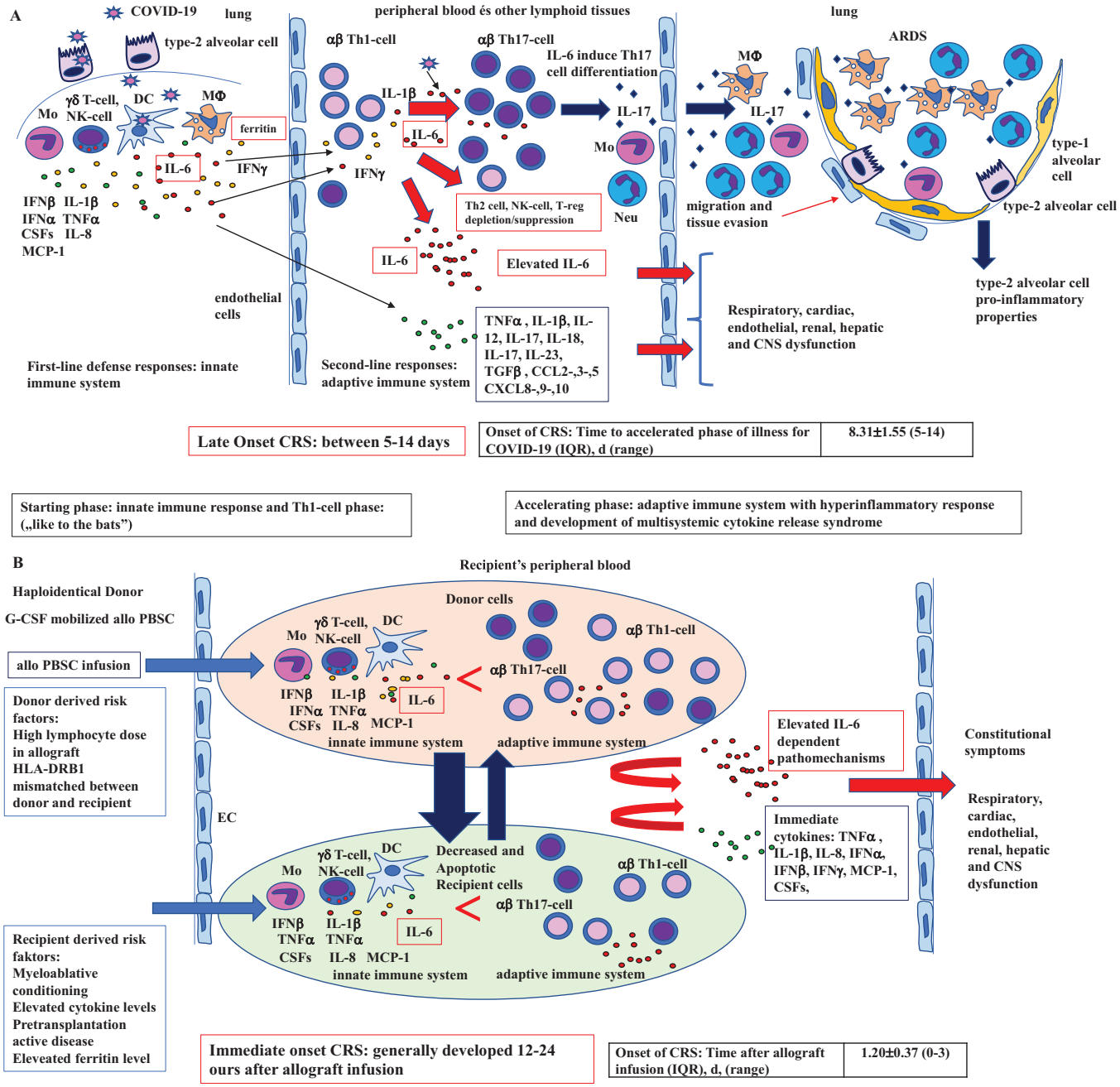


Fig. 4. Pathophysiological processes that lead to the development of severe CRS. (A) Main immunological steps and timely onset of/for the development of COVID-19 infection associated severe CRS („late onset CRS"). (B) Main risk factors, immunological findings and timely onset of allogeneic, mainly haploidentical hematopoietic stem cell transplantation associated severe CRS („immediate onset CRS")
Abbreviation: Mo: monocyte; NK: natural killer; MΦ: macrophage; DC: dendritic cell; IFN: interferon; IL: interleukin; TNF: tumor necrosis factor; MCP-1-/CCL2: monocyte chemoattractant protein-1/C-C motif chemokine ligand 2; CSFs: colony-simulating factors; Th: T-helper; T-reg: T regulator cells; Neu: neutrophil granulocyte; TGF: transforming growth factor; CCL: C-C motif chemokine ligand; CXCL: C-X-C motif chemokine; CNS: central nervous system; sCRS: severe cytokine release syndrome; G-CSF: granulocyte-colony-stimulating factor; PBSC: peripheral blood stem cells; HLA-DRB1: human leukocyte antigen-DRB1.

were highly similar. However, significant IL-6 elevation in COVID-19 sCRS group occurred only around day 7 following TCZ treatment. This is in accordance with the later onset of CRS in COVID-19 patients. Alike to the observations of *Murthy* et al. [5] ferritin levels remained significantly higher for a prolonged period in the allogeneic-HSCT group. The cause of this is unknown and remains to be clarified. Ferritin is a marker of macrophage, hepatocyte and eventually myeloid cell activation. According to COVACTA trial data elevated ferritin levels were associated with a better 28-day clinical outcome in patients receiving TCZ [33]. Even following successful treatment in the

allogeneic-HSCT group ferritin levels remained significantly high for a prolonged time period. As shown above, allogeneic HSCT associated CRS induces a definitely wider cytokine response and in this setting mechanisms of ferritin regulation may be more complex than previously suspected.

Serum levels of an array of cytokines/chemokines also show similar changes in allogeneic-HSCT- and COVID-19 sCRS: low values for IFNα2, IL-1α, IL-1β, IL-2, IL-4, IL-12, IL-13, IL-17A, TNFα, TNFβ and high values for IFNγ, IL-6, IL-8, RANTES, MCP-1, and IP-10. In addition, allogeneic-HSCT related sCRS affects a wider range of bioactive compounds as IL-5, IL-10, IL-15 are also substantially elevated (Fig. 2 and Table S2). In other publications IL-6, TNFα, IL-2, IL-7, IL-10, G-CSF, IP-10, MCP1, MIP-1α were found to be increased in severe COVID-19 cases [32]. *Murthy* et al. [5] detected an increase of IL-6, IL-10, IFNγ, MCP-1 and GM-CSF in allogeneic-HSCT associated CRS. It is important to mention however, that the number and composition of measured cytokines varies in different articles and our measurements may not show full alignment with the results of other investigators. Figure 5 illustrates possible receptor and signal transduction inhibitory treatment options in COVID-19 sCRS based on multi-cytokine patterns. In COVID-19 sCRS with elevated IL-8, MCP-1, IP-10, IFNγ, IL-6 and RANTES receptor antagonist or ligand blocking therapy is only available for the latter three bioactive compounds.

Non-selective small molecule anti-JAK/STAT compounds effectively inhibit intracellular signal transduction of IL-6 and many other cytokines. This means that their spectrum of effect is potentially broader than that of anti-IL-6 receptor antibodies. Anti-JAK/STAT therapy effectively inhibits the activity of the hyperactive immune system at several points providing rationale for their use in the management of sCRS [17]. Intracellular JAK/STAT signal transduction plays a key role in the mechanism of action of IFNα2, IFNγ, IL-2, Il-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL-15, TNFα, and TNFβ [34] (Fig. 5). Inhibitors of JAK/STAT pathway, however, do not affect activation pathways of IP-10, MCP-1 and RANTES which are potential driver factors in the pathophysiology of sCRS. Nevertheless, inhibition of signal transduction pathways of certain non-elevated cytokines can also be influenced by JAK/STAT inhibitors. Six elevated cytokines are likely to be driver cytokines in the development of CRS. Treatment with TCZ with ruxolitinib or baricitinib consolidation leads complete inhibition of the IL-6 and IFNγ pathways, however, the other four driver cytokine activation pathways remain intact and uninfluenced (Fig. 5). These varied intracellular pathways of cytokines and chemokines and their inhibitors might explain therapy unresponsiveness of certain combination therapies of some patients. Nevertheless, a very important message of our study is that we successfully applied two anti-JAK/STAT drugs (ruxolitinib and baricitinib) in four critically ill patients for the consolidation of previous TCZ treatment.

With regard to non-elevated cytokines in our patient case series many have an existing receptor antagonist or a blocker and some have a signal transduction inhibitor but most of them are not drivers of the pathological process. An exception may be the IL-1 pathway, which may be active even at very low cytokine levels. Contrary to the results of previous studies, we could not detect elevated levels of IL-1 and IL-17A [34, 35]. We speculate that a rise in their level is transient and short-lived in the very early phase of CRS. Rapid onset sCRS develops following the infusion of an average of $2x10^8$/kg CD3+ donor T-cells [5]. Despite immediate sampling after allogeneic-HSCT we were unable detect elevated IL-1 and IL-17A levels. Similar to this, we could not detect higher levels of these cytokines even in sHLH, GVHD and graft rejection (our observation, data not shown).

We also compared data from our retrospective cohort analysis of COVID-19 versus allogeneic-HSCT with COVID-19 versus CAR-T-cell CRS data published by *Hong* et al. [36] (Table S3). Age of patients was significantly higher in both COVID-19 CRS groups ($P < 0.001$ and $P = 0.004$) with a male predominance. Hypertension was also higher in the COVID-19 cCRS groups but was significant only when compared to the CAR-T-cell group ($P < 0.001$). The main symptom of CRS in all cohorts was fever but maximum temperature was higher in the CAR-T-cell and allogeneic-HSCT CRS groups. Cough was a major symptom in the COVID-19 CRS group (95% and 94%). Hypoxemia was observed basically in all patents in COVID-19 and allogeneic-HSCT sCRS compared to the CAR-T-cell cohort. On the other hand, hypotension was definitely significant in the CAR-T-cell ($P < 0.001$) and allogeneic-HSCT ($P = 0.036$) sCRS cohorts. The occurrence of capillary-leak syndrome was specific for allogeneic-HSCT sCRS ($P < 0.001$). The number of grade 4 CRS was significantly higher in the COVID-19 sCRS group ($P = 0.008$) compared to the CAR-T-cell sCRS cohort. We also observed a trend in our patient population towards a higher rate of grade 4 CRS in COVID-19 patients compared to allogeneic-HSCT sCRS (47% vs 27%). Maximal increase in CRP ($P=0.033$), D-dimer ($P < 0.001$), and ferritin ($P < 0.001$) values was significantly more pronounced in the CAR-T-cell group. In our patient population CRP, D-dimer and ferritin showed a clear increase but their maximum values did not differ significantly. As highlighted earlier however, in the allogeneic HSCT group ferritin levels remained elevated for a prolonged period and the difference to other sCRS groups was significant.

In their multi-cytokine screening study *Hong* et al. [36] reported that maximum values of IL-2 ($P < 0.001$), IL-6 ($P < 0.001$), IL-10 ($P < 0.001$) and IFNγ ($P < 0.001$) were significantly higher in the CAR-T-cell group. Similar to this, higher levels IL-2, IL-6, IL-10 and IFNγ were measured in the allogeneic-HSCT sCRS group compared to COVID-19 sCRS, however, the values did not show a significant difference. The level of IL-2 was significantly higher in the CAR-T-cell sCRS cohort compared COVID-19 group ($P < 0.001$). Values of this cytokine in the allogeneic HSCT group fell into the upper segment of the normal range and tended to be higher than those in the COVID-19 sCRS group. The increase in TNFα was significant between CAR-T-cell versus COVID-19 sCRS ($P < 0.001$) groups, however, even higher

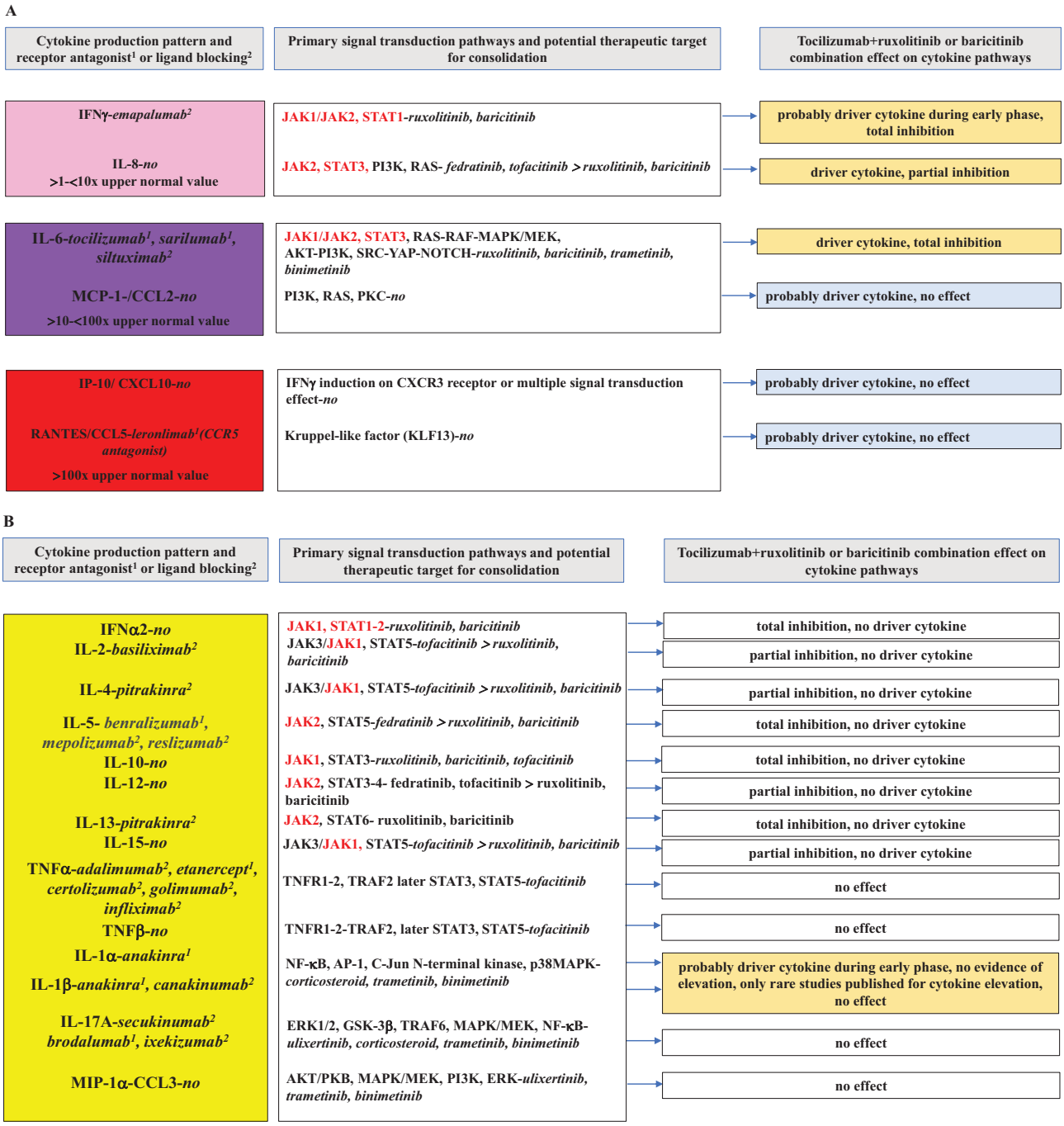


Fig. 5. They are therapeutic targets for multi-cytokines involved in the formation or progression of COVID-19 CRS and inhibition of cytokine receptor signaling and intracellular signaling mechanisms. (A) The role of elevated cytokine levels in the development of COVID-19 sCRS. Inhibition of driver cytokines is essential in inhibiting cytokine storm. (B) For low levels cytokine profiles, no driver cytokines are found except for the controversial IL-1.

When monotherapy inhibits Il-6 receptors, many cytokine activation cascades remain unresized, such as IFN-γ, IL-8, IP-10, MCP-1 and RANTES. The increase in IL-1 levels has not been found in our study, but the use of receptor antagonists has been shown to be effective in clinical trials. Il-1 levels are likely to rise in a very short period of time during the starting phase. Furthermore, IL-1 receptor activation requires IL-α, IL-1-β, IL-1-receptor and IL-1-receptor antagonist, so the process is very complex. On this basis, inhibition of a cytokine receptor does not provide adequate protection in the treatment of CRS. The situation is quite different when we target the inhibition of transduction molecules after receptor activation. JAK1/JAK2 inhibitor ruxolitinib/baricitinib inhibits many of the signaling mechanism of wide-spectrum cytokine. The use of a combination of IL-6 receptor inhibition and inhibitor JAK1/JAK2 is a realistic argument for treating CRS, but it can still be seen that there are bypass activation pathways-driver cytokines such as MCP-1, IP-10 and RANTES. As it stands, complete transduction inhibition cannot be achieved by the currently available treatment methods. In a given individual, the cytokine profile determines the method of treatment used.

values were measured in allogeneic-HSCT sCRS without significant difference compared to COVID-19 sCRS. The number of patients with respiratory failure and ICU admission rates was significantly higher in the COVID-19 sCRS cohort than in the CAR-T-cell group ($P < 0.001$). Oxygen support was required in all COVID-19 and allogeneic-HSCT sCRS patients which was clearly different from the CAR-T-cell (100% vs 34.1%, $P < 0.001$) group. There was no clear difference in corticosteroid treatment, but it was used most in the allogeneic-HSCT sCRS group. In the study of *Hong* et al. [36] study TCZ was used only in the CAR-T-cell sCRS cohort (65.9% vs 0%, $P < 0.001$). In our sCRS patient populations the proportion of TCZ treated patients was 100% in both groups. *Hong* et al. [36] did not provide a consolidation treatment after the administration of TCZ. In our allogeneic-HSCT sCRS group, however, 93% ($P < 0.001$) of patients received consolidative treatment (PTCY+tacrolimus+MMF) as an integral part of the stem cell transplant protocol for GVHD prevention. It is noteworthy that 4 (24%) of our COVID-19 patients with grade 4 CRS received TCZ+JAK/STAT inhibitor therapy and all recovered. Long-term survival was by far the best in the COVID-19 sCRS (100% and 88%) cohorts. Long-term survival in the CAR-T-cell sCRS cohort was 65.9% and it was by far the worst in the allogeneic-HSCT (33%, $P = 0.003$) sCRS cohort.

To this date, results of 9 randomized clinical trials (RCT) using TCZ in COVID-19 patients have been published, while data of the REMDACTA study are only available as a Google post [11, 37–44]. A significant reduction in 28-day mortality was demonstrated in three RCTs [11, 41, 42]. In other four RCTs no such benefit could be confirmed while no data were given in one study [37–40, 43]. A reduction of mechanical ventilation or progression to intensive care has been confirmed in four RCTs [11, 38, 40, 41] but could not be proven in further four [37, 39, 43, 45]. No data are available for the additional one trial [42]. Hospitalization period decreased with TCZ based therapy in four RCTs [11, 40, 42, 43]. Finally, results of the RECOVERY trial were decisive to prove the unequivocal benefit of TCZ in the management of COVID-19 associated sCRS [11]. In severe COVID-19 infection, TCZ reduced mortality by one third and the need for mechanical ventilation by almost half if the patient was oxygen dependent and CRP was 75 ≥ mg/L [11].

As of today, results of 23 retrospective cohort studies on TCZ have been published [45–47]. Five retrospective studies were conducted on a total of 655 critically ill COVID-19 patients who received TCZ [46, 49–52]. A decrease in mortality was reported by 4 retrospective studies [46, 49, 50, 52]. Pronounced benefit was reported by 2 studies where CRP was above 150 mg/L [48, 52]. Interpretation of the results may be influenced by the fact that only a single dose of TCZ was used in 4 studies [49–52]. A total of 1805 patients receiving TCZ were enrolled in 18 retrospective studies on severe COVID-19 patients [45, 47, 48]. Mortality reduction was shown only in 9 studies [53–61]. A comprehensive overview of the pathophysiological role of IL-6 in autoimmune inflammatory processes and CRS and the results of anti-IL-6 in CAR-T cell treatment and COVID-19 infection is available by *Kishimoto* [31]. Another meta-analysis found that TCZ reduces short-term mortality and reduces the need for mechanical ventilation [62].

Up till now, there has been no unequivocal opinion regarding the effective dose of TCZ. However, based on the experience gained from CAR-T-cell therapy, two doses appear to be more effective [23, 24, 31]. Although RCT data on the dose of TCZ are not available, it is likely that the appropriate dose is 8 mg/kg for two consecutive days. Depending on the clinical condition an additional third dose may be given in the next 24–36 hours. In agreement with other investigators our therapeutic results indicate that TCZ should be administered early in grade 2 with comorbidity and grade 3 CRS [7, 26, 27]. With the early administration of TCZ in adequate doses we could reverse further deterioration of 9 patients (grade 2 with comorbidity and grade 3) and prevent their progression to intensive treatment.

The effectiveness of ruxolitinib has been studied in 5 studies on a total of 533 patients [63–67]. Significant mortality reduction of severe COVID-19 patients was reported by only 1 non-randomized study [64]. *La Rosée* et al. [65] administered ruxolitinib to 14 patients with COVID-19-associated sCRS and documented sustained clinical improvement in 11 individuals. The randomized RUXCOVID trial on severe patients showed no effect on mortality and the RUXCOVID-DEVENT trial was discontinued on critical COVID-19 patients [67, 68]. *Cao* et al. [63] conducted a prospective phase II trial to compare ruxolitinib plus standard of care (SOC) versus placebo plus SOC in severe COVID-19 patients. Investigators observed a

(Fig. 5. continued) Color coding: yellow background: decreased value; blue background: normal value; pink background: >1-<10x upper normal value; purple background: >10-<100x upper normal value; red background: >100x upper normal value.
Abbreviations: sCRS: severe cytokine release syndrome; MoAb: monoclonal antibody; IFN: interferon; IL: interleukin; TNF: tumor necrosis factor; IP-10/CXCL10: interferon γ-induced protein 10 kDa/C-X-C motif chemokine 10; MCP-1-/CCL2: monocyte chemoattractant protein-1/C-C motif chemokine ligand 2; RANTES/CCL-5: regulated upon activation, normal T cell expressed and secreted/C-C motif chemokine ligand 5; MIP-1α-CCL3: macrophage inflammatory protein-1α/C-C motif chemokine ligand 3; JAK: Janus kinase inhibitor; STAT: signal transducer and activator of transcription; RAS: type of small GTP-binding protein; RAF: serine/threonine protein kinase; MAPK: mitogen-activated protein kinase; MEK: serine/tyrosine/threonine kinase; AKT: PI3K-Akt signaling pathway serine/threonine kinase; PI3K: phosphatidylinositol 3-kinase; SRC-YAP: SRC proto-oncogene, nonreceptor tyrosine kinase-Yes-associated protein; NOTCH: Notch signaling pathway; TNFR1-2: TNF receptor 1-2; TRAF-2: TNF receptor-associated factor 2; CXCR3: C-X-C motif chemokine receptor 3; PKC: protein kinase C; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; AP-1: activator protein-1; ERK: extracellular signal-regulated kinase; GSK-3β: glycogen synthase kinase-3β; PKB: protein kinase B.

shortened time to clinical improvement including CT signs, lymphopenia and levels in a 7-cytokine panel in the ruxolitinib arm but mortality was not affected. There is currently no clear conclusion on the use of ruxolitinib.

Baricitinib's treatment results were fairly impressive based on 6 studies [12, 69–73]. In the randomized Adaptive COVID-19 Treatment Trial 2 (ACTT-2) the baricitinib+remdesivir combination significantly reduced the need for mechanical ventilation and ICU progression and showed a tendency towards 28-day mortality reduction [69]. Based on the results of the trial the baricitinib+remdesivir combination was approved by the FDA and Emergency Use Authorization (EUA) was granted [69]. More recent results have been provided by the COV-BARRIER trial in which baricitinib significantly reduced mortality [70]. Based on a COV-BARRIER clinical trial, the FDA has approved baricitinib alone to treat a serious or critical COVID-19 infection treated in a hospital [74]. Overall, baricitinib significantly reduced ICU progression and mortality in 4 of the 5 currently available trials (796 patients) [69–73]. A small case series and case reports have been published on the combination of TCZ and JAK/STAT inhibitors. *Rosas* et al. [14] treated 60 patients with TCZ or baricitinib and 11 patients were treated with a combination of the two drugs. The study did not reach a definitive conclusion but the combination of TCZ+baricitinib did not cause serious side effects. *Portsmore* et al. [75] successfully used ruxolitinib in combination with TCZ in 2 patients with severe COVID-19 related sHLH. In another case report, patients with chronic GVHD after allogeneic transplant were successfully treated with a combination of TCZ+ruxolitinib [76]. In agreement with *Rosas* et al. [14] opinion we recommend the early use of these drugs and their combined consolidative administration. With regard to the more than 100 times elevated level of RANTES we propose that it may be a driver cytokine in COVID-19-associated sCRS. The possible role of the RANTES inhibitor leronlimab, the IL-1 inhibitor anakinra or canakinumab, as well as TNFα inhibitors is still being investigated in clinical trials for the treatment of COVID-19 infection and its complications [34, 35, 77].

CONCLUSIONS

Our study has several limitations. Firstly, it is a retrospective and observational study with a small number of patients with two different backgrounds of sCRS. However, in seems to be indisputable that COVID-19- and allogeneic-HSCT sCRS can only be compared retrospectively. Secondly, only a small number of sCRS cases were available for both groups. Cases of allogeneic-HSCT sCRS were selected from more than 300 transplanted individuals, depending on donor type and GVHD prevention strategies. Data from the published literature also report on small numbers of sCRS patients in the allogeneic, mainly haploidentical settings. COVID-19 sCRS patients with the corresponding number of cases were selected from the first wave of pandemic affecting Hungary at the start of the CONTRAST study.

To the best of our knowledge, this is the first retrospective cohort study to compare the characteristics of sCRS induced by COVID-19 infection and allogeneic-HSCT. Our data may help to provide new insight into the understanding of pathophysiology and innovative treatment options of COVID-19-associated sCRS. We propose that the cytokine/chemokine release pattern of allogeneic-HSCT and COVID-19 associated sCRS are highly similar and internationally accepted grading systems can be applied for both conditions [7, 24]. In allogeneic-HSCT-associated sCRS a broader spectrum of cytokines are expressed. CRS begins over the course of a relatively short period of clinical deterioration with a simultaneous rise of IL-6 and other significant laboratory parameters. Once patients enter this phase, anti-IL-6 therapy should be initiated as soon as possible. A single dose anti-IL-6 antibody and corticosteroid therapy for the treatment of higher-grade sCRS patients may be suboptimal and insufficient. Therefore, we recommend that two or in selected cases three doses of TCZ should be used in proper quantities. The effect of anti-IL-6 monoclonal antibody therapy can be successfully consolidated with JAK/STAT inhibitors. We believe that combined induction and consolidation treatment should be used in both sCRS forms. Our results were generated on a limited patient cohort in a single institution and they have to be confirmed on a higher number of patients in well-designed clinical investigations.

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AUTHOR CONTRIBUTIONS

Dr L. Gopcsa had full access to all of the data in this study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Concept and design*: Drs I. Vályi-Nagy, L. Gopcsa, P. Reményi. J. Sinkó. Drs I. Bobek, G. Bekő, B Lakatos, E Molnár, M Réti, P Reményi, János Sinkó, János Szlávik, Gábor Tatai, contributed equally to the study.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1556/030.2021.01620.

REFERENCES

1. Abboud R, Keller J, Slade M, DiPersio JF, Westervelt P, Retting MP, et al. Severe cytokine-release syndrome after T cell-replete peripheral blood haploidentical donor transplantation is associated with poor survival and anti-IL-6 therapy is safe and well tolerated. Biol Blood Marrow Transpl 2016; 22: 1851–60.
2. Imus PH, Blackford AL, Bettinotti M, Luznik EJ, Fuchs CA, Huff DE, et al. Severe cytokine release syndrome after haploidentical peripheral blood stem cell transplantation. Biol Blood Marrow Transpl 2019; 25: 2431–7.
3. Albanyan O, Kim S, Deol A, Alavi AD, Kin LJ, Ayash V, et al. Grade III-IV cytokine release syndrome is associated with inferior survival in patients undergoing haploidentical donor stem cell transplant. J Clin Oncol 2020; 38: 7546.
4. Solán L, Landete E, Bailén R, Dorado G, Oarbeascoa J, Anguita JL, et al. Cytokine release syndrome after allogeneic stem cell transplantation with posttransplant cyclophosphamide. Hematol Oncol 2020; 38: 597–603.
5. Murthy H, Iqbal H, Chavez JC, Kharfan-Dabaja MA. Cytokine release syndrome: current perspectives. Immunotargets Ther 2019; 8: 43–52.
6. Schots R, Kaufman L, Van Riet I, Ben Othman T, De Waele M, Van Camp B, et al. Proinflammatory cytokines and their role in the development of major transplant-related complications in the early phase after allogeneic bone marrow transplantation. Leukemia 2003; 17: 1150–6.
7. Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014; 124: 188–95.
8. Le RQ, Li L, Yuan W, Shord SS, Nie L, Habtemariam, et al. FDA approval summary: tocilizumab for treatment of chimeric antigen receptor T cell-induced severe or life-treatening cytokine release syndrome. Oncologist 2018; 23: 943–7.
9. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. The Lancet 2020; 395: 1033–134.
10. Wei Q, Lin H, Wei R-G, Chen N, He F, Zou D-H, et al. Tocilizumab treatment for COVID-19 patients: a systematic review and meta-analysis. Infect Dis Poverty 2021; 10: 71. Available from: https://doi.org/10.1186/s40249-021-00857-w.
11. Recovery Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomized, controlled, open-label, platform trial. Lancet 2021; 397: 1637–45. Available from: https://doi.org/10.1016/S0140-6736(21)00676-0.
12. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-drug-treatment-covid-19/ [Accessed 24 Jun 2021].
13. https://www.ema.europa.eu/en/news/ema-starts-evaluating-use-roactemra-hospitalised-adults-severe-covid-19/ [Accessed 16 Aug 2021].
14. Rosas J, Liaño FP, Cantó ML, Barea JMC, Beser AR, Rabasa JTA, et al. Experience with the use of baricitinib and tocilizumab monotherapy or combined, in patients with interstitial pneumonia secondary to coronavirus COVID19: a real-world study. Reumatol Clin 2020; S1699-258X(20)30271-0. Available from: https://doi.org/10.1016/j.reuma.2020.10.009.
15. Riegler LL, Jones GP, Lee DW. Current approaches in the grading and management of cytokine release syndrome after chimeric antigen receptor T-cell therapy. Ther Clin Risk Manag 2019; 15: 323–35.
16. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, Stemmler HJ, Schlöber HA, Schlaak M, et al. Cytokine release syndrome. J Immunother Cancer 2018; 6: 56. Available from: https://doi.org/10.1186/s40425-018-0343-9.
17. Luo W, Li Y-X, Jiang L-J, Chen Q, Wang T, Ye D-W. Targeting JAK-STAT signaling to control cytokine release syndrome in COVID-19. Trends Pharmacol Sci 2020; 41: 531–43.
18. Lakatos B, Szabó BG, Bobek I, Gopcsa L, Bekő G, Kiss-Dala N, et al. Laboratory parameters predicting mortality of adult in-patients with COVID-19 associated cytokine release syndrome treated with high-dose tocilizumab. Acta Microbiol Immunol Hung 2021; 68: 145–52. Available from: https://doi.org/10.1556/030.2021.01526.
19. Bobek I, Gopcsa L, Réti M, Bekő G, Hancz L, Lakatos B, et al. Successful administration of convalescent plasma in critically ill COVID-19 patients in Hungary: the first two cases. Orvosi Hetilap 2020; 161: 1111–21.
20. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395: 1054–62.
21. Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci U S A 2020; 117: 10970–5.
22. Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol 2014; 66: 2613–20.
23. Neelapu SS, Tummala S, Kebriaei P, Wierda W, Gutierrez, Locke FL, et al. Chimeric antigen receptor T-cell therapy-assessment and management of toxicities. Nat Rev Clin Oncol 2018; 15: 47–62.
24. Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transpl 2019; 25: 625–38.
25. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19. J Infect 2020; 80: 607–13.
26. Prilutskiy A, Kritselis M, Shevtsov A, Yambayev I, Vadlamudi C, Zhao Q, et al. SARS-CoV-2 infection-associated hemophagocytic lymphohistiocytosis. Am J Clin Pathol 2020; 154: 466–74.
27. Li MY, Li L, Zhang Y, Wang XS. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. Infect

Dis Poverty 2020; 9: 45. Available from: https://doi.org/10.1186/s40249-020-00662-x.
28. Chen X, Zhao B, Qu Y, Chen Y, Xiong J, Feng Y, et al. Detectable serum SARS-CoV-2 viral load (RNAaemia) is closely associated with drastically elevated interleukin 6 (IL-6) level in critically ill COVID-19 patients. Clin Infect Dis 2020; 71: 1937. Available from: https://doi.org/10.1093/cid/ciaa449.
29. Banerjee A, Baker ML, Kulcsar K, Misra V, Plowright R, Mossman K. Novel insights into immune systems of bats. Front Immunol 2020; 11: 26. Available from: https://doi.org/10.3389/fimmu.2020.00026.
30. Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the perspective of clinical immunologists from China. Clin Immunol 2020; 214: 108393. Available from: https://doi.org/10.1016/j.clim.2020.108393.
31. Kishimoto T. IL-6: from arthritis to CAR-T-cell therapy and COVID-19. Int Immunol 2021; 33: 515–9. Available from: https://doi.org/10.1093/intimm/dxab011.
32. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497–506.
33. Tom J, Bao M, Tsai L, Qamra A, Summers D, Triguero MC, et al. Prognostic and predictive biomarkers in patients with COVID-19 treated with tocilizumab in a randomized controlled trial. medRxiv 2020. Available from: https://doi.org/10.1101/2020.12.23.20247379.
34. Rizk JG, Kalantar-Zadeh K., Mehra MR, Lavie CJ, Rizk Y, Forthal DN. Pharmaco-immunomodulatory therapy in COVID-19. Drugs 2020; 80: 1267–92.
35. Langer-Gould A, Smith JB, Gonzales EG, Castillo RD, Figueroa JG, Ramanathan A, et al. Early identification of COVID-19 cytokine strom and treatment with anakinra or tocilizumab. Int J Infect Dis 2020; 99: 291–7.
36. Hong R, Zhao H, Wang Y, Chen Y, Cai H, Hu Y, et al. Clinical characterization and risk factors associated with cytokine release syndrome induced by COVID-19 and chimeric antigen receptor T-cell therapy. Bone Marrow Transpl 2021; 56: 570–80.
37. Salvarani C, Dolci G, Massari M, Merlo DF, Cavuto S, Savoldi L, et al. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia. A randomized clinical trial. JAMA Intern Med 2020; 181: 24–31.
38. Hermine O, Mariette X, Tharaux PL, Resche-Rigon M, Porcher R, Ravaud P, et al. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia. A randomized clinical trial. JAMA Intern Med 2020; 181: 32–40.
39. Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, et al. Efficacy of tocilizumab in patients hospitalized with Covid-19. N Engl J Med 2020; 383: 2333–44.
40. Rosas IO, Bräu N, Waters M, Go RC, Hunter BD, Bhagani S, et al. Tocilizumab in hospitalized patients with severe COVID-19 pneumonia. N Engl J Med 2021; 384: 1503–16.
41. Salama C, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, et al. Tocilizumab in patients hospitalized with Covid-19 pneumonia. N Engl J Med 2021; 384: 20–30.
42. REMAP-CAP Investigators, Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, et al. Interleukin-6 receptor antagonists in critically ill patients with COVID-19. N Engl J Med 2021; 384: 1491–502.
43. Veiga VC, Prats JAGG, Farias DLC, Rosa RG, Dourado LK, Zampieri FG, et al. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. BMJ 2021; 372: n84. Available from: https://doi.org/10.1136/bmj.n84.
44. https://clinicaltrials.gov/ct2/show/NCT04409262/ [Accessed 11 Mar 2021].
45. Tleyjeh MI, Kashour Z, Damlaj M, Riaz M, Tlayjeh H, Altannir M, et al. Efficacy and safety of tocilizumab in COVID-19 patients: a living systematic review and meta-analysis. Clin Microbiol Infect 2021; 27: 215–27.
46. Gupta S, Wang W, Hayek SS, Chan L, Mathews KS, Melamed ML, et al. Association between early treatment with tocilizumab and mortality among critically ill patients with COVID-19. JAMA Intern Med 2020; 181: 41–51.
47. Vu CA, DeRonde KJ, Vega AD, Maxam M, Holt G, Natori Y, et al. Effects of tocilizumab in COVID-19 patients: a cohort study. BMC Infect Dis 2020; 20: 964. Available from: https://doi.org/10.1186/s12879-020-05701-4.
48. Cavalli G, Larcher A, Tomelleri A, Campochiaro C, Della-Torre E, De Luca G, et al. Interleukin-1 and interleukin-6 inhibition compared with standard management in patients with COVID-19 and hyperinflammation: a cohort study. Lancet Rheumatol 2021; 3: e253–61. Available from: https://doi.org/10.1016/S2665-9913(21)00012-6.
49. Somers E, Eschenauer GA, Troost JP, Golob JL, Gandhi TN, Wang L, et al. Tocilizumab for treatment of mechanically ventilated patients with COVID-19. Clin Infect Dis 2020; 73: e445–54. Available from: https://doi.org/10.1093/cid/ciaa954.
50. Ramaswamy M, Mannam P, Comer R, Sinclair E, McQuaid DB, Schmidt ML. Off-label real wold experience using tocilizumab for patients hospitalized with COVID-19 disease in a regional community healt system: a case-control study. medRxiv 2020. Available from: https://doi.org/10.1101/2020.05.14.20099234.
51. Eimer J, Vesterbacka J, Svensson A-K, Stojanovics B, Wagrell C, Sönnerborg A, et al. Tocilizumab shortens time on mechanical ventilation and length of hospital stay in patients with severe COVID-19: a retrospective cohort study. J Intern Med 2021; 289: 434–6.
52. Biran N, Ip A, Ahn J, Go RC, Wang S, Mathura S, et al. Tocilizumab among patients with COVID-19 in the intensive care unit: a multicentre observational study. Lancet Rheumatol 2020; 2: e603–12. Available from: https://doi.org/10.1016/S2665-9913(20)30277-0.
53. De Rossi NC, Scarpazza C, Filippini C, Cordioli C, Rasia S, Mancinelli CR, et al. Early use of low dose tocilizumab in patients with COVID-19: a retrospective cohort study with a complete follow-up. EClinicalMedicine 2020. Available from: https://doi.org/10.1016/j.eclinm.2020.100459.
54. Guaraldi G, Meschiari M, Cozzi-Lepri A, Milic J, Tonelli R, Menozzi M, et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. Lancet Rheumatol 2020; 2: e474–84. Available from: https://doi.org/10.1016/S2665-9913(20)30173-9.
55. Narain S, Stefanov DG, Chau AS, Weber AG, Marder G, Kaplan B, et al. Comparative survival analysis of immunomodulatory therapy for COVID-19 'cytokine storm'. Chest 2020; 159: 933–48.

56. Mikulska M, Nicolini LA, Signori A, Di Biagio A, Sepulcri C, Russo C, et al. Tocilizumab and steroid treatment in patients with COVID-19 pneumonia. PLos One 2020; 15: e0237831. Available from: https://doi.org/10.1371/journal.pone.0237831.
57. Moreno-García E, Rico V, Albiach L, Agüero D, Ambrosioni J, Bodro M, et al. Tocilizumab is associated with reduced risk of ICU admission and mortality in patients with SARS-CoV-2 infection. medRxiv 2020. Available from: https://doi.org/10.1101/2020.06.05.20113738.
58. Gokhale Y, Mehta R, Kulkarni U, Karnik N, Gokhale S, Sundar U, et al. Tocilizumab improves survival in severe COVID-19 pneumonia with persistent hypoxia: a retrospective cohort study with follow-up from Mumbai, India. BMC Infect Dis 2021; 21: 241. Available from: https://doi.org/10.1186/s12879-021-05912-3.
59. Rossi B, Nguyen LS, Zimmermann P, Boucenna F, Dubret L, Baucher L, et al. Effect of tocilizumab in hospitalized patients with severe pneumonia COVID-19: a cohort study. medRxiv 2020; 13: 317. Available from: https://doi.org/10.3390/ph13100317.
60. Rossotti R, Travi G, Ughi N, Corradin M, Baiguera C, Fumagalli R, et al. Safety and efficacy of anti-il6-receptor tocilizumab use in severe and critical patients affected by coronavirus disease 2019: a comparative analysis. J Infect 2020; 81: e11–7. Available from: https://doi.org/10.1016/j.jinf.2020.07.008.
61. Roumier M, Paule R, Vallée A, Rohmer J, Ballester M, Brun A-L, et al. Tocilizumab for severe worsening COVID-19 pneumonia: a propensity score analysis. J Clin Immunol 2021; 41:303–14.
62. Snow TAC, Saleem N, Ambler G, Nastouli E, Singer M, Arulkumaran. Tocilizumab in COVID-19: a meta-analysis, trial sequential analysis, and meta-regression of randomized-controlled trials. Intensive Care Med 2021; 47: 641–52.
63. Cao Y, Wei J, Zou L, Jiang T, Wang G, Chen L, et al. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): a multicenter, single-blind, randomized controlled trial. J Allergy Clin Immunol 2020; 146: 137–46.
64. D'Alessio A, Del Poggio P, Bracchi F, Cesana G, Sertori N, Di Mauro D, et al. Low-dose ruxolitinib plus steroid in severe SARS-CoV-2 pneumonia. Leukemia 2021; 35: 635–8.
65. La Rosée F, Bremer HC, Gehrke I, Kehr A, Hochhaus A, Birndt S, et al. The Janus kinase 1/2 inhibitor ruxolitinib in COVID-19 with severe systemic hyperinflammation. Leukemia 2020; 34: 1805–15.
66. Vannucchi AM, Sordi B, Morettini A, Nozzoli C, Poggesi L, Pieralli F, et al. Compassionate use of JAK1/2 inhibitor ruxolitinib for severe COVID-19: a retrospective observational study. Leukemia 2021; 35: 1121–33.
67. https://clinicaltrials.gov/ct2/show/NCT04362137/ [Accessed 02 Jun 2021].
68. https://clinicaltrials.gov/ct2/show/NCT04377620/ [Accessed 15 Mar 2021].
69. Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. N Engl J Med 2021; 384: 795–807.
70. Marconi VC, Ramanan AV, de Bono S, Kartman CE, Krishnan V, Liao R, et al. Efficacy and safety of baricitinib for the treatment of hospitalized adults with COVID-19 (COV-BARRIER): a randomized, double-blind, parallel-group, placebo-controlled phase 3 trial. Lancet Respir Med 2021; S2213-2600(21)00331–3. Available from: https://doi.org/10.1016/S2213-2600(21)00331-3.
71. Rodriguez-Garcia JL, Sanchez-Nievas G, Arevalo-Serrano J, Garcia-Gomez C, Jimenez-Vizuete JM, Martinez-Alfaro E, et al. Baricitinib improves respiratory function in patients treated with corticosteroids for SARS-CoV-2 pneumonia: an observational cohort study. Rheumatology 2021; 60: 399–407.
72. Stebbing J, Nievas GS, Falcone M, Youhanna S, Richardson P, Ottaviani S, et al. JAK inhibition reduces SARS-CoV-2 liver infectivity and modulates inflammatory responses to reduce morbidity and mortality. Sci Adv 2021; 7: eabe4724. Available from: https://doi.org/10.1126/sciadv.abe4724.
73. Cantini F, Niccoli L, Nannini C, Matarrese D, Di Natale ME, Lotti P, et al. Beneficial impact of baricitinib in COVID-19 moderate pneumonia; multicentre study. J Infect 2020; 81: 647–79.
74. https://www.fdanews.com/articles/203760-fda-changes-eua-so-olumiant-can-stand-alone-in-treating-covid-19?v=preview [Accessed 28 Jul 2021].
75. Portsmore S, Nguyen TNT, Beacham E, Neelakantan P. Combined IL-6 and JAK/STAT inhibitor therapy in COVID-19-related sHLH, potential game changer. Br J Haematol 2020; 190: 525–8.
76. Innes AJ, Cook LB, Marks S, Bataillard E, Crossette-Thambiah, Sivasubramaniam G, et al. Ruxolitinib for tocilizumab-refractory severe COVID-19 infection. Br J Haematol 2020; 190: e198–200. Available from: https://doi.org/10.1111/bjh.16979.
77. Patterson BK, Seethamraju H, Dhody K, Corley MJ, Kazempour K, Lalezari JP, et al. Disruption of the CCL5/RANTES-CCR5 pathway restore immune homeostasis and reduces plasma viral load in critical COVID-19. medRxiv 2020. Available from: https://doi.org/10.1101/2020.05.02.02.20084673.