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Short Communication

Cenicriviroc for the treatment of COVID-19: first interim results of a randomised, placebo-controlled, investigator-initiated, double-blind phase II trial

Florian Kurth[a,b,1,*], Elisa T. Helbig[a,1], Lena J. Lippert[a,1], Charlotte Thibeault[a], Gianluca Barbone[c], Marius A. Eckart[c], Martin Kluge[c], Tobias Puengel[c], Münevver Demir[c], Robert Röhle[d,e], Theresa Keller[d], Christoph Ruwwe-Glösenkamp[a], Martin Witzenrath[a,f], Norbert Suttorp[a], Christof von Kalle[g], Leif E. Sander[a], Christoph Jochum[c], Frank Tacke[c,**]

[a] *Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Infectious Diseases and Respiratory Medicine, Berlin, Germany*
[b] *Department of Tropical Medicine, Bernhard Nocht Institute for Tropical Medicine and Department of Medicine I, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany*
[c] *Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Hepatology and Gastroenterology, Berlin, Germany*
[d] *Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Institute of Biometry and Clinical Epidemiology, Berlin, Germany*
[e] *Berlin Institute of Health at Charité – Universitätsmedizin Berlin, Berlin, Germany*
[f] *German Centre for Lung Research (DZL), Gießen, Germany*
[g] *Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Clinical Study Centre (CSC), Berlin, Germany*

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ABSTRACT

Objectives: C-C-chemokine receptors (CCRs) are expressed on a variety of immune cells and play an important role in many immune processes, particularly leukocyte migration. Comprehensive preclinical research demonstrated CCR2/CCR5-dependent pathways as pivotal for the pathophysiology of severe COVID-19. Here we report human data on use of a chemokine receptor inhibitor in patients with COVID-19.
Methods: Interim results of a 2:1 randomised, placebo-controlled, investigator-initiated trial on the CCR2/CCR5-inhibitor Cenicriviroc (CVC) 150 mg BID orally for 28 d in hospitalised patients with moderate to severe COVID-19 are reported. The primary endpoint is the subject's responder status defined by achieving grade 1 or 2 on the 7-point ordinal scale of clinical improvement on day 15.
Results: Of the 30 patients randomised, 18 were assigned to receive CVC and 12 to placebo. Efficient CCR2- and CCR5 inhibition was demonstrated through CCL2 and CCL4 elevation in CVC-treated patients (485% and 80% increase on day 3 compared to the baseline, respectively). In the modified intention-to-treat population, 82.4% of patients (14/17) in the CVC group met the primary endpoint, as did 91.7% (11/12) in the placebo group (OR = 0.5, 95% CI = 0.04–3.41). One patient treated with CVC died of progressive acute respiratory distress syndrome, and the remaining had a favourable outcome. Overall, treatment with CVC was well tolerated, with most adverse events being grade I or II and resolving spontaneously.

* Corresponding author. Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Infectious Diseases and Respiratory Medicine, Augustenburger Platz 1, 13353 Berlin, Germany
** Alternative corresponding author. Mailing address: Charité – Universitätsmedizin Berlin, Department of Hepatology and Gastroenterology, Campus Virchow-Klinikum and Campus Charité Mitte, Augustenburger Platz 1, 13353 Berlin, Germany
E-mail addresses: florian.kurth@charite.de (F. Kurth), frank.tacke@charite.de (F. Tacke).
[1] These authors contributed equally, ordered by seniority

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Conclusions: Our interim analysis provides proof-of-concept data on CVC for COVID-19 patients as an intervention to inhibit CCR2/CCR5. Further studies are warranted to assess its clinical efficacy.

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic has challenged healthcare systems worldwide, with only dexamethasone widely adopted for clinical management [1]. A dysregulated innate immune response, specifically C–C motif chemokine ligand 2 (CCL2)-mediated recruitment of macrophages to the lung, is a key pathophysiological factor in severe COVID-19 [2]. The C-C chemokine receptor type 2 (CCR2)/CCR5 inhibitor Cenicriviroc (CVC), developed against human immunodeficiency virus and inflammatory steatohepatitis, has had a favourable safety-profile in phase I-III trials and inhibits influx of inflammatory macrophages to the liver in animal models [3]. We hypothesised that CVC prevents CCL2/CCL3–5-mediated influx of inflammatory cells into lung tissue, thereby averting organ damage and disease progression in COVID-19.

We report interim results of an investigator-initiated, monocentre, randomised, placebo-controlled, double-blind phase II trial of CVC vs. standard of care in hospitalized COVID-19-patients at Charité – Universitätsmedizin Berlin, Germany.

2. Materials and methods

Hospitalised adults with PCR-confirmed, symptomatic SARS-CoV-2 infection were eligible for inclusion. Patients with critical disease (need for invasive mechanical ventilation, IMV) were not eligible. Other key exclusion criteria included pregnancy, liver cirrhosis Child B or C, stage ≥4 chronic kidney disease, and advanced cardiac disease (New York Heart Association [NYHA] III-IV). An independent pharmacy performed computer-generated block randomisation to CVC or placebo in a 2:1 ratio, stratified by: (I) disease severity (i.e. baseline score of 3 vs. 4–5 on the WHO 7-Point Ordinal Scale where 1 = not hospitalised, no limitations on activities; 2 = not hospitalised, limitation on activities; 3 = hospitalised, not requiring supplemental oxygen; 4 = hospitalised, requiring supplemental oxygen; 5 = hospitalised, on non-invasive ventilation or high flow oxygen devices; 6 = hospitalised, on invasive mechanical ventilation or extracorporeal membrane oxygenation, 7 = death), and (II) presence or absence of at least one of the following comorbidities: (i) diabetes mellitus, (ii) obesity (body mass index (BMI) >30 kg/m2), (iii) chronic obstructive pulmonary disease (COPD) or asthma, and (iv) heart failure (NYHA Class I or II)). This resulted in four strata (score 3 and none of the mentioned comorbidities; score 3 and any of the mentioned comorbidities; score 4 or 5 and none of the mentioned above comorbidities; score 4 or 5 and any of the mentioned comorbidities) with equal assignment to treatment or placebo.

Patients were treated with a loading dose of 300 mg CVC orally followed by 150 mg twice daily for 28 d plus standard of care. Patients were followed weekly until day 29 and once on day 85. Primary endpoint was the subject's responder status, defined by achieving grade 1–2 on the WHO 7-point ordinal scale on day 15, i.e. hospital discharge. Secondary endpoints included time to improvement, days spent in hospital or in ICU, duration of need for supplemental oxygen, oxygen-free days, number of adverse events (AEs) and serious AEs (SAEs), and course of inflammatory markers. Exploratory endpoints comprised course of serum cytokine and chemokine levels, and semiquantitative SARS-CoV-2 status on days 8 and 15.

A total sample size of 186 patients was determined to detect a greater than 20% increase in responder status (60% vs. 81%) on day 15 with 85% power and 1% dropout-rate. A prespecified interim analysis (local type-1 error rate according to O'Brien Fleming [4] approx. 10^{-6}) after inclusion of 30 participants was demanded for safety purposes by the ethics committee of Landesamt für Gesundheit und Soziales, Berlin. Except for an independent statistician, all study staff and patients remained blinded.

We report descriptive statistics for both groups, i.e. means and standard deviation (SD) or medians and interquartile range (IQR), and proportions for the pre-specified study endpoints in the safety-population (patients who received at least one dose of study drug) and the modified intention-to-treat (mITT) population (safety population without patients whose study treatment was stopped due to IMV, as per protocol). Firth's logistic regression was used to calculate the odds ratio with 95% confidence interval for the primary outcome. In compliance with the vote of the Ethics Committee, no effect sizes for secondary outcomes were included in this interim analysis.

The trial was conducted in accordance with the declaration of Helsinki and principles of Good Clinical Practice, registered at EudraCT (2020–001493–29) and clinical-trials.gov (NCT04500418, first posted August 5, 2020), and approved by the ethics committee of Landesamt für Gesundheit und Soziales, Berlin. All patients gave written informed consent to participate. The trial protocol is available from the investigators upon request.

3. Results

Between 1 September and 29 December 2020, 31 patients were included, of whom one withdrew consent prior to any study related procedures (see patient flow chart provided as Supplementary Fig. S1). Baseline characteristics were comparable between both treatment-groups except for a higher prevalence of pulmonary comorbidities, slightly higher COVID-19 severity at inclusion, and lower median age in the CVC-group (Table 1, Fig. 1A).

One participant in the CVC group had progressive acute respiratory distress syndrome (ARDS) with need of IMV on day 5. As per protocol, the study drug was discontinued, and the patient was excluded from the mITT group. Two further patients in the CVC group required high-flow oxygen therapy from day 1 and 2, respectively, but neither progressed to needing IMV. In the mITT population, 86.2% of patients reached the primary endpoint, 82.4% (14/17) in the CVC group and 91.7% (11/12) in the placebo group (Odds Ratio = 0.5 (95% confidence interval 0.04–3.41) (Table 2). CVC-treated patients spent a median of 7 d (IQR 5; 10 d) in hospital and placebo-treated patients were discharged after a median of 6 d (IQR 3.8; 7.2 d). The duration of need for supplemental oxygen after randomization was median 5 d (IQR 3; 9 d) for CVC-treated patients compared with a median of 3.5 d (IQR 1; 5 d) for placebo-controlled patients. Details on secondary clinical outcomes are described in Table 2.

Inflammatory markers decreased rapidly and similarly in both groups (Fig. 1C, D; Supplementary Fig. S2A, B). CVC treated pa-

Table 1
Baseline characteristics of the modified intention-to-treat population

Characteristics		CVC (n = 17)	Placebo (n = 12)	Total (N = 29)
Age (years), median (IQR)		57 (55; 70)	63.5 (56; 70.8)	61 (55; 70)
Sex, n (%)				
	Female	3 (17.6)	2 (16.7)	5 (17.2)
	Male	14 (82.4)	10 (83.3)	24 (82.8)
BMI (kg/m^2), median (IQR)		29.3 (26; 32.9)	26.9 (25.7; 31.7)	28.2 (25.8; 32.9)
Comorbidities, n (%)				
	BMI > 30 kg/m^2	8 (47.1)	4 (33.3)	12 (41.4)
	Asthma or COPD	4 (23.5)	0 (0.0)	4 (13.8)
	NYHA I or II	1 (5.6)	0 (0.0)	1 (3.4)
Baseline score on 7-Point ordinal scale, n (%)				
	3	3 (17.6)	3 (25.0)	6 (20.7)
	4	13 (76.5)	9 (75.0)	22 (75.9)
	5	1 (5.9)	(0)	1 (3.4)
Treated with dexamethasone, n (%)		12 (70.6)	7 (58.3)	19 (65.5)
Days from symptom onset to admission, median (IQR)		6 (5; 9.7)	7.7 (5.6; 9.8)	7.4 (5.3; 9.8)
Days from symptom onset to randomisation, median (IQR)		8.8 (6.5; 11.5)	9.2 (6.8; 10.8)	8.8 (6.8; 11.5)
Days from admission to randomisation, median (IQR)		1.5 (1; 2)	1.2 (1; 2)	1.5 (1; 2)
CRP (mg/L), mean (SD)		98.82 (45.17)	74.75 (61.91)	88.86 (53.08)
PCT (ng/mL), mean (SD)		0.11 (0.06)	0.14 (0.1)	0.12 (0.08)
IL-6 (ng/L), mean (SD)		60.64 (74.8)	34.12 (43.52)	49.66 (64.17)
Ferritin (ng/mL), mean (SD)		937.01 (380.14)	1144.27 (709.04)	1021.45 (536.19)

BMI, body mass index; CRP, C-reactive protein; CVC, Cenicriviroc; IL-6, interleukin-6; IQR, interquartile range; PCT, procalcitonin; SD, standard deviation.

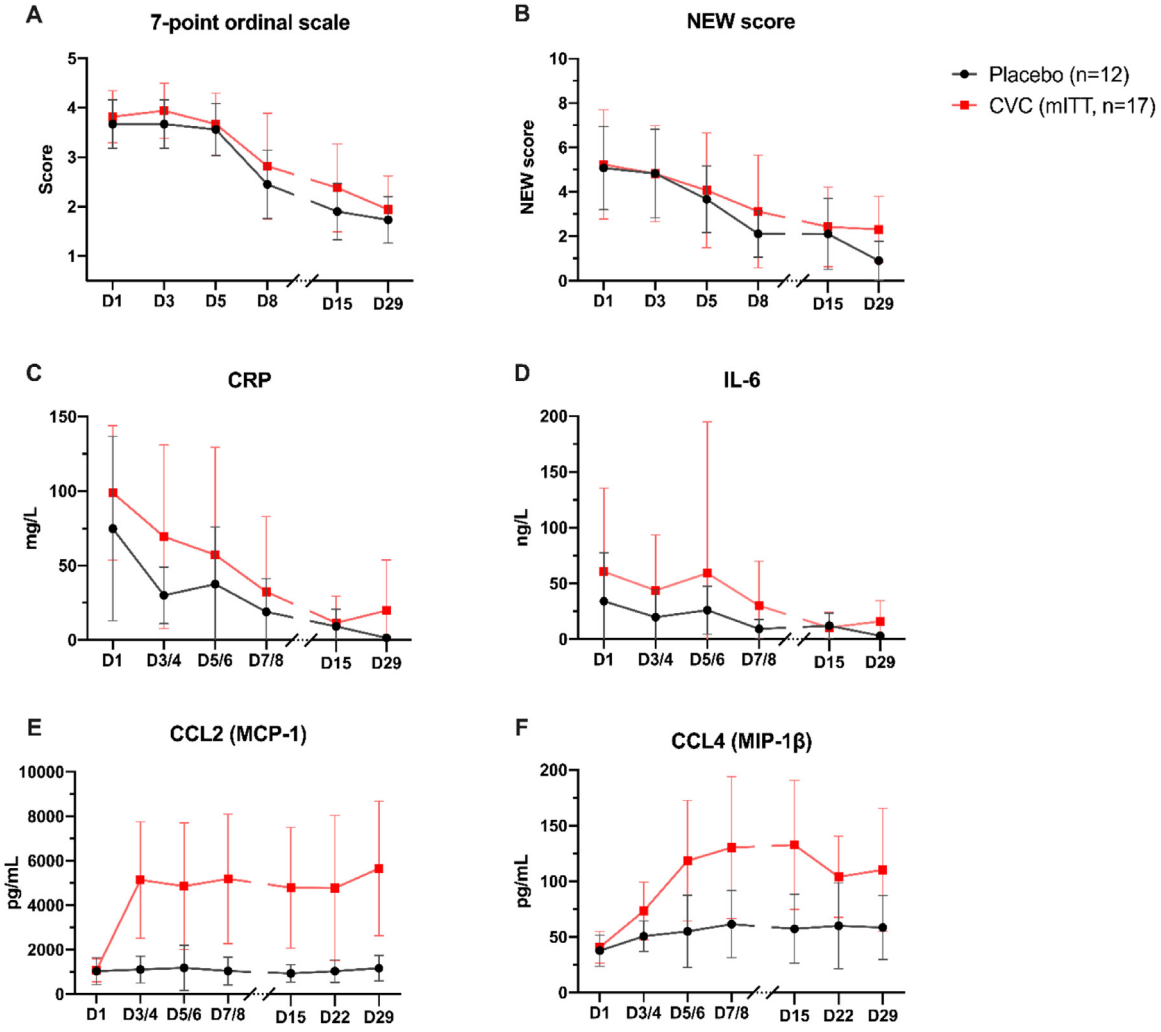

Fig. 1. Trajectories of disease severity scores using 7-point ordinal scale (A) and NEW Score (B), CRP (C), IL-6 (D), CCL2 (E), and CCL4 (F) for CVC- or placebo-treated patients (modified intention-to-treat population, n = 17 and n = 12, respectively). Data shown as mean ± standard deviation over time, with day 1 (D1) representing baseline at day of inclusion.
CCL, C-C motif chemokine ligand; CRP, C-reactive protein; IL, interleukin; NEW, national early warning; MCP-1, monocyte chemoattractant protein-1; MIP-1β, macrophage inflammatory protein 1β.

Table 2
Outcome in the modified intention-to-treat population

Outcome		CVC (n = 17)	Placebo (n = 12)	Total (N = 29)	Odds Ratio (95% CI)
Primary Endpoint					
	Score of "1" or "2" on 7-point ordinal scale, n (%)	14 (82.4)	11 (91.7)	25 (86.2)	0.5 (0.04–3.41)
Secondary Endpoints					
	Days to improvement of 1 or 2 points on 7-point ordinal scale, median (IQR)	7 (4; 9)	6.5 (4.5; 7)	7 (4; 7)	[a]
	Days spent in hospital, median (IQR)	7 (5; 10)	6 (3.8; 7.2)	6 (5; 9)	[a]
	Days spent in ICU, median (IQR)	0 (0; 0)	0 (0; 0)	0 (0; 0)	[a]
	Days with supplemental oxygen after randomisation	5 (3; 9)	3.5 (1; 5)	4 (1; 7)	[a]
	In-hospital days with supplemental oxygen, median (IQR)	7 (4; 10)	5.5 (1; 7)	6 (2; 9)	[a]
	Exogenous oxygen free days in the first 28 d, median (IQR)	23 (19; 25)	24.5 (23; 27)	24 (21; 27)	[a]

CI, confidence interval; CVC, Cenicriviroc; ICU, intensive care unit; IQR, interquartile range.
[a] Odds Ratio was not calculated for secondary outcomes according to the statistical analysis plan of the interim analysis in compliance with the vote of Ethics Committee.

tients showed an increase of CCL2 and CCL4 (485% and 80% increase on day 3 compared to the baseline, respectively; Fig. 1E, F), clearly indicating CCR2/5 target engagement with the applied dosages. There was no compensatory induction of IL-8 or other chemotactic factors (Supplementary Fig. S2 C–I), and we did not observe prolonged SARS-CoV-2 shedding (i.e., SARS-CoV-2 viral load was negative or above a cycle-threshold of 30 for 29/29 (100%) patients on day 15) or bacterial superinfection associated with the immune-modulatory treatment.

CVC was well tolerated by study participants and there were no drug related SAEs. AEs were frequent, occurring in 18/18 (100%) patients in the CVC-group and 11/12 (91.7%) patients in the placebo-group (Supplementary Table S1). Whereas most AEs were mild (grade I-II) and resolved spontaneously, we observed three possibly drug-related AEs with severity grade 3 in CVC-treated patients, one of which (QTc-prolongation) led to termination of the study drug. Most SAEs occurred in one patient with progressive ARDS and were judged to be related to COVID-19 and not associated with the study drug.

4. Discussion

Several studies have built a firm rationale for inhibition of CCR2-/CCR5-mediated inflammation in COVID-19 [2,5], e.g. a strong association has been observed between CCR2-expression and respiratory failure in lung tissue of intensive care unit patients [5]. Based on these findings and the known favourable safety profile of CVC [3], repurposing of CVC has been proposed for the treatment of COVID-19 and was amongst other drugs tested in the ACTIV-1 trial (NCT04593940). The trial has recently been completed; results are yet to be published.

Our data show an increase of CCL2/CCL4 from day 3 in CVC-treated patients, clearly indicating CCR2/5 target engagement. No firm conclusion on the efficacy of CVC can be derived from the data at this stage. Numerically there seems to be no difference between treatment groups regarding AEs, or primary or secondary endpoints. The number of patients who showed clinical deterioration was higher in the CVC than in the placebo group, yet the overall proportion of patients with progressive ARDS was substantially lower than in similar patient cohorts [6]. Given the inequalities regarding age, pulmonary comorbidity, and disease severity at baseline, we can only speculate whether CVC might have prevented progression to IMV in single patients. Also, more data is needed on treatment timing and possible synergistic effects with other immunomodulatory drugs. Of note, there is increasing evidence concerning the role of macrophages for long-term organ damage in COVID-19, with a potential for CVC in mitigating "long-COVID" symptoms or pulmonary fibrosis [7].

Our data support CVC as a promising candidate targeting the detrimental host response to SARS-CoV-2 and warrant further clinical testing in larger patient cohorts.

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Ethical approval

The trial was approved by the ethics committee of Landesamt für Gesundheit und Soziales, Berlin. All patients gave written informed consent to study participation.

Declaration of competing interest

None to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jgar.2022.12.004.

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