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SHORT COMMUNICATION

Feasibility of Continuous Infusion of Cefiderocol in Conjunction with the Establishment of Therapeutic Drug Monitoring in Patients with Extensively Drug-Resistant Gram-Negative Bacteria

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Abstract

Background and Objective Resistance to antibacterial substances is a huge and still emerging issue, especially with regard to Gram-negative bacteria and in critically ill patients. We report a study in six patients infected with extensively drug-resistant Gram-negative bacteria in a limited outbreak who were successfully managed with a quasi-continuous infusion of cefiderocol.

Methods Patients were initially treated with prolonged infusions of cefiderocol over 3 h every 8 h, and the application mode was then switched to a quasi-continuous infusion of 2 g over 8 h, i.e. 6 g in 24 h. Therapeutic drug monitoring (TDM) was established using an in-house liquid chromatography-tandem mass spectrometry (LC-MS/MS) method.

Results Determined trough plasma concentrations were a median of 50.00 mg/L [95% confidence interval (CI) 27.20, 74.60] and steady-state plasma concentrations were a median of 90.96 mg/L [95% CI 37.80, 124]. No significant differences were detected with respect to acute kidney injury/continuous renal replacement therapy. Plasma concentrations determined from different modes of storage were almost equal when frozen or cooled, but markedly reduced when stored at room temperature.

Conclusions (Quasi) continuous application of cefiderocol 6 g/24 h in conjunction with TDM is a feasible mode of application; the sample for TDM should either be immediately analyzed, cooled, or frozen prior to analysis.

Key Points

Our results provide insight into a pharmacokinetically optimized use of cefiderocol. The continuous application of cefiderocol in combination with therapeutic drug monitoring (TDM) allows plasma levels to remain above target MICs, while preventing unnecessary high peak levels caused by bolus application.

Therefore, continuous application of cefiderocol in conjunction with TDM is a feasible and pharmacologically and microbiologically beneficial mode of application; the sample for TDM should be cooled or frozen prior to analysis.

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1 Introduction

Enterobacterales resistant to carbapenem antibiotics (carbapenem-resistant enterobacterales [CRE]) are a serious health threat [1]. In addition to a markedly reduced choice of effective antimicrobials for treatment, the propensity of CREs for clonal expansion and spreading associated with healthcare is a serious concern. As an example, carbapenem-resistant *Klebsiella pneumoniae* was included in the World Health Organization (WHO) priority list of 'critical bacteria' [2, 3]. In addition to carbapenem resistance, enterobacterales often carry a number of additional resistance mechanisms, making them 'extensively drug resistant' [4]. The epidemiology of CREs is marked by large regional variations in prevalence. For example, CREs have a high prevalence in India, South America, and Eastern Europe [5, 6]. In these regions, up to 70% of *Klebsiella pneumoniae* are resistant to carbapenems. Therefore, transfer of patients from healthcare facilities from high-risk regions also involves the risk of transferring CREs to low-prevalence settings.

A frequent mechanism of carbapenem resistance is the expression of carbapenemases, which enzymatically inactivate a wide range of β-lactams, including carbapenems. An important subgroup of carbapenemases are members of the 'metallo-β-lactamase' (MBL) group of enzymes, also called Ambler class B [7]. Members of this group cannot be inhibited by clinically available β-lactamase inhibitors such as sulbactam, tazobactam, avibactam, relebactam, and vaborbactam. The monobactam molecule aztreonam is resistant to hydrolysis by MBL enzymes; however, it needs to be combined with a β-lactamase inhibitor to protect it from inactivation by other β-lactamases. The combination of aztreonam/avibactam has been studied in various case series [8], however no preparation is yet approved for clinical use.

Cefiderocol (Fetcroja®) is an innovative antimicrobial consisting of a modified cephalosporin structure with an added catechol moiety. This latter structure is capable of chelating iron molecules, allowing cefiderocol to cross the membrane of Gram-negative bacteria via iron transport channels ('Trojan horse' mechanism). Using this transport mechanism, cefiderocol avoids bacterial defense mechanisms such as efflux pumps, and, in the end, binds to the penicillin-binding protein (PBP3) [9–11]. Additionally, cefiderocol has high stability against various β-lactamases, including carbapenemases, due to modifications in side chains C-3 and C-7. Therefore, cefiderocol is an option for the treatment of CREs with MBLs [12–16].

During the first wave of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic in 2021, the Göttingen University Hospital received a patient from Romania with acute respiratory distress syndrome (ARDS) associated with coronavirus disease 2019 (COVID-19). The patient had been treated in the intensive care unit (ICU) and was placed on extracorporeal membrane oxygenation (ECMO) just before transport to Germany. Unfortunately, the patient was colonized with an extensively drug-resistant strain of *Klebsiella pneumoniae*, expressing New-Delhi metallo-β-lactamase (NDM). Despite precautionary measures, this led to a limited outbreak of CRE *Klebsiella pneumoniae* in the ICU.

During this outbreak, cefiderocol was the only available therapeutic option to treat infections with CRE *Klebsiella pneumoniae*. To optimize cefiderocol treatment, we instituted two measures. First, to ensure adequate dosing, we developed and implemented a protocol for therapeutic drug monitoring (TDM) of cefiderocol. Second, we administered cefiderocol with an extended (quasi-continuous) infusion. Since cefiderocol as a β-lactam exerts its action in a time-dependent manner [17], we therefore hypothesized that an extended infusion will increase the efficacy of its antimicrobial action.

We report on a study consisting of six patients who were treated with a quasi-continuous infusion of cefiderocol in conjunction with TDM, and describe the effect of different storage modalities on the determination of plasma concentrations.

2 Methods

At first, all patients received cefiderocol as an extended infusion of 3 h every 8 h for 24 h (i.e. three doses) consistent with the manufacturer's recommendation ("Administer 2 grams of Fetcroja® for injection every 8 hours by intravenous infusion (IV) for 3 hours in patients with creatinine clearance (CLcr) 60 to 119 mL/min."). Plasma samples were taken immediately prior to the application of the fourth dose of cefiderocol (that is, after 24 h of cefiderocol therapy) to establish the trough concentration. We then changed the application mode to continuous infusion, administering the daily dose of 6 g quasi-continuously over a period of 24 h (3 × 2 g over 8 h each) and taking blood samples 24 h after the start of the quasi-continuous infusion, i.e. at the end of three 8-h infusions. Note that stability of the infusion solution had only been demonstrated for 6 h at 25 °C, and prolonging the infusion could influence stability and antimicrobial efficiency.

Of the six patients included in this report, four patients started with a bolus of 2 g and continuous infusion immediately after the bolus, while the remaining two patients were accidentally started with continuous infusion without additional bolus administration. In particular, all of these patients had received bolus administration every 8 h the day before, i.e. continuous infusion started at least at a trough concentration. Blood samples were taken in a 7.5 mL S-Monovette® with a silicate clotting activator (Sarstedt AG & Co. KG, Nümbrecht, Germany). Immediately after drawing, the samples were transported to the Institute of Clinical Chemistry where they were centrifuged, and four aliquots were prepared from the serum supernatant. One aliquot was analyzed immediately (within 1 h of blood collection), while the remaining three were stored under different storage conditions for 24 h and then analyzed (one aliquot was stored at room temperature, one aliquot was cooled at 4–8 °C, and one aliquot was frozen at – 80 °C).

2.1 Bioanalytical Assay

To determine blood cefiderocol concentrations, stock solutions were prepared from two 1 g doses of cefiderocol (Fetcroja 1 g ch. –B:7001) in 0.9% sodium chloride (NaCl) and 3-(*N*-morpholino)propane sulfonic acid (MOPS) buffer. Based on this solution, the calibrator and control material were prepared in the expected concentration range (2.0; 20.0 and 200.0 mg/L for calibrators, and 10.0 and 100.0 mg/L for quality control [QC] samples) in drug-free serum, aliquoted and stored at − 80°C until use. A liquid chromatography-tandem mass spectrometry (LC-MS/

MS) method was established on our CLAM 2030 LCMS-8060NX equipped with a Nexera LC40 (Fa. Shimadzu Corporation). As a result of the structure of cefiderocol, we used 1% formic acid and methanol as mobile phases for chromatographic separation. MS and MS/MS data of the single- and double-protonated molecular ions of cefiderocol were acquired and multiple reaction monitoring (MRM) transitions for determination and quantification were optimized. Fragmentation patterns of single- and double-charged molecular ions were identified using high-resolution mass spectrometry. The most abundant fragment ions of the double-charged molecular ion are identical to the fragment ions obtained from the single-charged ion. Sample preparation was performed by CLAM2030: 20 µL methanol, 100 µL acetonitrile, 10 µL internal standard (D6-meropenem; 20 mg/L) and 20 µL sample were added to a filter, and the sample was vortexed and filtered; 0.5 µL of the mixture was injected into the LC-MS/MS system. A sharp step gradient from 0.3% methanol within 0.5 min to 70% methanol within 0.3 min was used for chromatographic separation on a UPLC BEH-C18-column (2.1*50; 1.8 µm; Waters Corporation). A flow rate of 0.5 mL/min was used. For cefiderocol (RT 1.42 min) *m/z* 376.7/214 and *m/z* 376.7/171, as well as an internal standard (RT 1.4 min) m/z 390.2/147.1, were used for quantification. Calibrator and QC concentrations were 2.0, 20.0, 200.0 mg/L and 10.0, and 100.0 mg/L, respectively. Linearity was tested from 2.0 to 200.0 mg/L. The QC precision between runs was 8.6% at 10 mg/L and 7.6 at 100.0 mg/L ($n = 20$), and was 3.9% and 4.0% within runs, respectively. The lower limit of quantitation (LLOQ) was determined at 1.0 mg/L (cv 4.5%). The extracted ion chromatograms of the patient sample and the QC sample are shown in the electronic supplementary data.

2.2 Microbiological Assessment

The identification of bacteria species was carried out using MALDI Biotyper 3.0 (Bruker Daltonics, Bremen, Germany). Antimicrobial susceptibility testing was based on VITEK 2 (bioMérieux, Marcy-l'Étoile, France) using AST-N214 for *Klebsiella pneumoniae* and AST-N248 for *Pseudomonas aeruginosa*. The detection of carbapenemases was carried out using the NG-Test Carba 5 assay (NG Biotech, Guipry, France) targeting five main carbapenemases: KPC-, NDM-, VIM-, IMP- ,and OXA-48-like. The detected carbapenemases were later confirmed with next-generation sequencing analyzed by the Institute for Infection Control and Infectious Diseases, University Medical Center Göttingen, Göttingen, Germany. The minimal inhibitory concentration (MIC) of cefiderocol was determined by cefiderocol MTS™ (MIC Test Strip, Liofilchem, range 0.016–256 mg/L) according to the manufacturer's instructions, and with Sensititre™ EUMDROXF broth microdilution (BMD) panels (ThermoFisher Diagnostics B.V., Landsmeer, The Netherlands; panel range 0.03–8 mg/L) using Sensititre™ Cation Adjusted Mueller–Hinton broth (ThermoFisher Diagnostics B.V.). MICs were interpreted using the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint table for enterobacterales and *Pseudomonas aeruginosa* [18]. For QC, the recommended strains ATCC 25922 *Escherichia coli* and ATCC 27853 *Pseudomonas aeruginosa* were used.

2.3 Statistical Analysis

Statistical analysis was performed using SPSS version 26.0 (IBM Corporation, Armonk, NY, USA). Data were tested for normal distribution using the Shapiro–Wilk test; differences between patients and storage conditions were tested using the Wilcoxon test; and differences in cefiderocol concentrations with respect to acute kidney injury (AKI; categorical) were tested using the Kruskal–Wallis test. Statistical significance was assumed at $p = 0.05$). Data are presented as median and 95% confidence interval. Informed consent was obtained from all patients and next of kin for off-label use and publication, respectively. This observational study was approved by the Institutional Review Board of Georg-August University Göttingen on 11 October 2021 (IRB No.: 32/8/21).

3 Results

We included six patients in this case-based observational study (see Table 1 for patient characteristics). Four patients survived and two patients died in the ICU; in one patient, care was withdrawn due to a pre-existing poor functional status, according to the patient's wishes, and the other patient died from recurrent severe infections that eventually led to unsalvageable multiorgan failure.

Trough plasma concentrations of the immediate analysis were 50.00 mg/L [CI 27.20–74.60] and steady-state plasma concentrations were 90.96 mg/L [CI 37.80–124.00] (Table 2). The differences between the trough and steady-state concentrations were not statistically significant ($p = 0.437$). No statistical differences were detected with respect to AKI/continuous renal replacement therapy (CRRT), most likely due to a lack of statistical power (Fig. 1 clearly illustrates that patients with the lowest glomerular filtration rate [GFR] had the highest concentrations).

Plasma concentrations determined from different storage modes were almost equal when frozen or cooled, but markedly reduced when stored at room temperature (frozen

Table 1 Patient characteristics

Patient no.	Age, years	Sex	GFR [mL/min]	Bodyweight [kg]	Pathogen	Outcomes
1[a,b]	48	Male	56	61	*Klebsiella pneumoniae*	Deceased in ICU
2[a,b]	55	Male	17	80	*Klebsiella pneumoniae*	Survived to discharge
3	63	Male	74	90	*Klebsiella pneumoniae*	Survived to discharge
4[a,b]	45	Male	18	110	*Klebsiella pneumoniae*	Survived to discharge
5	54	Male	102	75	*Pseudomonas aeruginosa*	Survived to discharge
6[b]	48	Female	132	95	*Klebsiella pneumoniae*	Deceased in ICU
Median [95% CI]	51 [48, 55]		65 [18, 102]	85 [75, 95]		

CRRT continuous renal replacement therapy, *GFR* glomerular filtration rate, *CI* confidence interval, *ICU* intensive care unit

[a]Acute kidney injury/CRRT

[b]Bolus application just before the start of the continuous infusion

Table 2 Plasma concentrations (mg/L) of cefiderocol immediately before and after 24 h of continuous infusion; determination within 1 h of drawing the sample

Patient no.	Prior to 3-h infusion (2 g) ['trough']	Immediately after 3-h infusion (2 g) ['peak']	After 24 h of continuous infusion (6 g) ['steady-state']
1[a]	125.55	228.43	25.2
2[a]	69.05	149.0	135.61
3	27.2	114.44	37.8
4[a]	74.6	140.54	117.75
5	30.95	153.57	124
6[a]	25.95	NA	64.18
Median [95% CI]	50.00 [27.20, 74.60]	144.77 [134.75, 153.57]	90.96 [37.80–124.00]

CI confidence interval, *NA* not available

[a]Bolus application just before the start of the continuous infusion

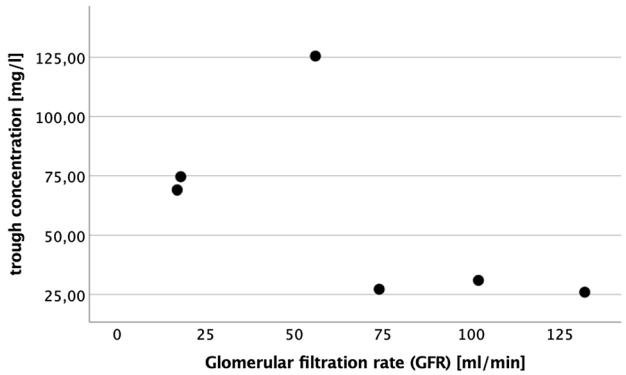

Fig. 1 Scatterplot of trough concentration versus glomerular filtration rate that clearly shows that patients with high GFR had low trough concentrations and vice versa

91.45 mg/L [CI 37.80–124.00], standard deviation [SD] 52.46; cooled 117.91 mg/L [CI 43.70–134.52], SD 50.45; room temperature 65.18 mg/L [CI 32.12–87.89], SD 32.63) (Table 3).

Klebsiella pneumoniae with expression of OXA-48-like and NDM-type carbapenemases was identified in respiratory samples of all patients. In patient six, an intra-abdominal infection caused by the outbreak strain of *Klebsiella pneumoniae* was the initial source of infection. All strains were extensively drug-resistant, but susceptible to cefiderocol. The MICs for cefiderocol ranged between 0.75 and 1 mg/L. According to EUCAST, the clinical breakpoint for cefiderocol is established at 2 mg/L for enterobacterales [18]; therefore, for treatment, serum concentrations of 8 mg/L were assumed to be effective [19, 20].

4 Discussion

Cefiderocol is a new and valuable treatment option for enterobacterales with resistance to carbapenems. This is particularly relevant when carbapenem resistance is caused by MBLs. Critical illness is marked by profound changes in the pharmacokinetics of many drugs, including antimicrobials.

Table 3 Steady-state plasma concentrations (mg/L) of cefiderocol after 24 h of storing at the respective conditions

Patient no.	Room temperature	Refrigerator (4–8 °C)	Frozen (− 80 °C)
1	14.27	24.16	25.2
2	87.89	134.52	136.61
3	32.12	43.70	37.8
4	85.15	108.14	117.75
5	65.18	127.67	124
6	NA	130	65.15
Median [95% CI]	65.18 [32.12, 87.89]	117.91 [43.70, 134.52]	91.45 [37.80, 124.00]
SD	32.63	50.45	52.46

CI confidence interval, *NA* not available, *SD* standard deviation

Alterations in fluid distribution caused by capillary leakage and infusion treatment increase the volume of distribution (Vd), which is particularly relevant for hydrophilic compounds [21]. Cefiderocol as a hydrophilic antibiotic has a relatively low Vd of 18 L, and therefore pathophysiological changes caused by critical illness can lead to a decrease in antibiotic concentrations [22–25]. Furthermore, protein loss is a regular finding in critically ill patients, and hypoalbuminemia (< 25 g/L) is detected in 40–50% of intensive care patients [26, 27]. This alteration will have an effect on the pharmacokinetics of antibiotics with high to medium plasma protein binding (PPB), such as cefiderocol, with PPB of 40–60%. A reduced PPB increases the proportion of unbound or 'free' drug molecules (= active), which unfortunately enhances its elimination. Together, both an increase in Vd and a decrease in PPB can potentially decrease plasma drug concentrations of cefiderocol [28]. This effect is further aggravated by its short elimination half-life of 2–3 h [24]. It is well established that these metabolic or pharmacokinetic alterations can cause widely divergent plasma antimicrobial concentrations after standard doses [29]. These considerations make the 'blind' administration of antimicrobials (i.e. without TDM) unreliable and difficult to predict [30, 31]. Therefore, extended or continuous administration of β-lactams with additional TDM is an attractive option to optimize pharmacokinetics/pharmacodynamics in critically ill patients [30–32]. These statements are the reason for the unexpected values for patient number 1, who had a significantly lower Vd than the other patients in our study (8 L vs. 14.5 L [mean]) as well as a significantly reduced plasma albumin level (1.4 g/dL).

Currently, the manufacturer recommends a 2 g dose of cefiderocol every 8 h, administered as an extended infusion over 3 h [33]. As a β-lactam antibiotic, the bactericidal effect of cefiderocol depends on the time that the drug concentration remains above the MIC of the respective bacterium [34]. In turn, subtherapeutic plasma concentrations increase the risk of therapeutic failure and may select bacterial resistance [35]. In a recently published case series, optimal cefiderocol pharmacokinetics/pharmacodynamics could not be achieved in most patients using the recommended dose [36]. Steady-state plasma concentrations in our study were measured at 90.96 mg/L, well above the assumed sufficient target of 8 mg/L (four times higher than the clinical breakpoint set by EUCAST), even at the lowest value determined (25.2 mg/L).

Furthermore, an initial loading dose followed by extended infusion has been recommended to optimize the bactericidal effect and improve the results for treatment with β-lactam antibiotics [32, 37]. In our study, in those patients where no initial boluses were administered, plasma concentrations after continuous application of 6 g for 24 h were measured at 80.90 mg/L [37.80–124.00], which is still much higher than the target of 8 mg/L. Therefore, our results could question the necessity of applying a bolus prior to the initiation of a continuous infusion of cefiderocol; however, when using a lower continuous dose, a loading dose might be reasonable. To further judge this, more TDM time points must be evaluated.

As cefiderocol is almost entirely excreted through the kidneys (renal excretion 98.6%, unchanged 90.6%), it is recommended the dose be adjusted for patients with renal impairment [38]. Especially in those patients, TDM is of extraordinary importance. However, we did not find statistically significant differences between patients with normal kidney function and patients with AKI/CRRT. This finding also needs to be validated in larger patient collections.

In our limited cohort, continuous application of 6 g of cefiderocol for 24 h resulted in plasma concentrations almost 12 times higher than the target concentration. It is well established that bacterial killing is not improved by concentrations greater than 4–6 times the respective MICs of β-lactams [34, 39]. Therefore, a dose reduction guided by TDM might be possible in some patients. We did not adjust the doses of cefiderocol in our study as this would have been an intervention rather than an observation and would require a different study design. However, the published adverse events during cefiderocol treatment were mild to moderate [40, 41] and we considered that high plasma concentrations

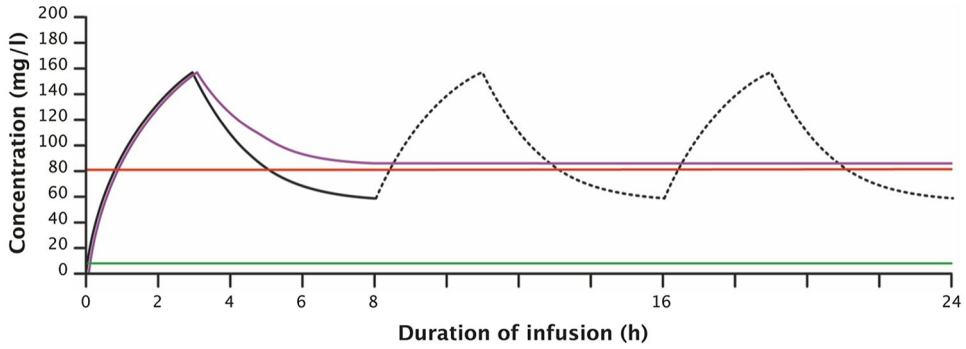

Fig. 2 Explicative diagram of the concentration curves of cefiderocol administration based on study data where available (bold lines), otherwise extrapolated (dotted lines) for reasons of convenience. the green line represents 4 × MIC; black curve represents intermittent, prolonged bolus administration; violet curve represents continuous administration with the initial bolus; and the red line represents continuous administration without an initial bolus. *MIC* minimal inhibitory concentration

were not excessively harmful to our patients. Although all plasma concentrations measured in this study were higher than likely necessary, extremely high peak concentrations, as detected after intermittent bolus dosing, could be avoided by continuous infusion (Fig. 2).

An additional result of our trial is that the samples were not stable when stored at room temperature. There were no differences in drug concentrations when the samples were stored at 4–8°C or frozen at − 80°C. The results show that to measure the correct plasma concentrations of the cefiderocol sample, it should be immediately cooled; if stored longer, it should be frozen.

4.1 Limitations

We report a very small number of patients from a single tertiary center. This makes our results prone to bias and they should be verified in a mixed population, multicenter setting, and randomized design. Furthermore, the analytical method we used is not fully validated (calibration curve using infusion solution, no interlaboratory comparison). However, the deviation when using the infusion solution compared with the pure substance is usually < 10% and therefore can be used. Furthermore, our results are comparable with previously published results of cefiderocol TDM and therefore appear plausible. As only limited sampling points were evaluated with TDM, we cannot exclude fluctuations in plasma concentrations between these instances. However, subtherapeutic drug concentrations between the available sampling points seem unlikely given the high plasma concentrations at 24 h of quasi-continuous infusion without a dosing gap. To further elucidate this, more TDM time points would be needed in both continuous and intermittent applications, and these aspects should be part of future research.

5 Conclusion

In view of the increasing number of extensively drug-resistant, Gram-negative bacteria, cefiderocol is an important weapon in the treatment of serious infections. Our results provide insight into pharmacokinetically optimized use of cefiderocol. The continuous application of cefiderocol in combination with TDM allows plasma concentrations to remain above target MICs, while preventing excessively high peak concentrations caused by bolus application. As it included only a small cohort of patients, our study should be viewed as a baseline for further investigation to explore the implications of clinically significant patient-centered outcomes in the context of randomized controlled trials.

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Declarations

Authors' contributions Conceptualization: CP and LOH. Data curation: CP and LOH. Formal analysis: CP, FS, and LOH. Investigation: FS. Methodology: CP, FS, AD, and LOH. Project administration: LOH. Resources: JS, MB, UG, and KM. Supervision: JS, MB, UG, KM, and OM. Validation: JS, UG, KM, and OM. Visualization: CP and CS. Writing – original draft: CP and LOH. Writing – review and editing: FS, CS, AD, CL, JS, MB, UG, KM, and OM.

Conflicts of interest Carolin Prinz, Frank Streit, Christian Schumann, Anna Dudakova, Uwe Groß, Matthias Bohn, Julie Schanz, Christian Lanckohr, and Konrad Meissner report no conflicts of interest. Lars-Olav Harnisch has received honoraria for educational lectures from

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Ethics approval The study was approved by the Institutional Review Board of Georg–August University Göttingen on 11 October 2021 (IRB No.: 32/8/21). All procedures in this study were in accordance with the 1964 Helsinki declaration (and its amendments), and the details of the Ethics Committee or Institutional Review Board that approved the study.

Consent to participate/publish Written informed consent was obtained for off-label use and publication from all patients and legal representatives, respectively

Code availability Not applicable.

Data availability statement All data generated or analyzed during this study are included in this published article

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