recent publications (6–8). Pan and colleagues evaluated the potential for lung recruitment (as the recruitment-to-inflation ratio) in COVID-19 ARDS. The researchers found that lung recruitability was generally poor on the first day of observation but increased by alternating the prone and supine positions (8). This can be easily explained by the appearance of basilar consolidation over the course of COVID-19 ARDS. This consolidation accounts for 13–53% of the CT patterns, depending on when the scan is performed; the later the CT scan, the more frequent the consolidation (9, 10). In the present study, the predominant pattern in COVID-19 ARDS was diffuse ground-glass opacity, together with alveolar consolidation in about 60% of cases. This consolidation might be explained by the long median (IQR) time interval between the onset of symptoms and orotracheal intubation (10 [7–15] d) in our study population. Other studies have reported similar findings, but we cannot rule out the possible occurrence of "patient self-inflicted lung injury" due to excessive breathing efforts and delayed intubation (4, 7).

Our study had some important limitations. First, the study population was small and we did not prespecify the target sample size. Second, we only assess basic respiratory mechanical variables; the comparison of advanced parameters (such as transpulmonary pressures or ventilation–perfusion mismatches) might have revealed additional intergroup differences.

Conclusions

The main features of respiratory mechanics, the response to treatment (such as the oxygenation response to LRMs or prone position), and prognosis are similar in COVID-19 and non–COVID-19 ARDS. The oxygenation response to LRM and a high PEEP appear to be very heterogeneous in COVID-19 ARDS; this would argue in favor of a personalized ventilation strategy. ■

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Complement Inhibition with the C5 Blocker LFG316 in Severe COVID-19

To the Editor:

In critically ill patients with coronavirus disease (COVID-19), a hyperinflammatory host response contributes to organ dysfunction and death. The role of complement in these events is unclear. Complement activation yields powerful proinflammatory effectors, notably C5a and membrane attack complex, and triggers coagulation (1); it has been implicated in bacterial sepsis and septic shock, sepsis-like syndromes associated with coronavirus infections, and COVID-19–associated microvascular injury and thrombosis (2–4). Recently, the C5a/C5aR1 axis was implicated in

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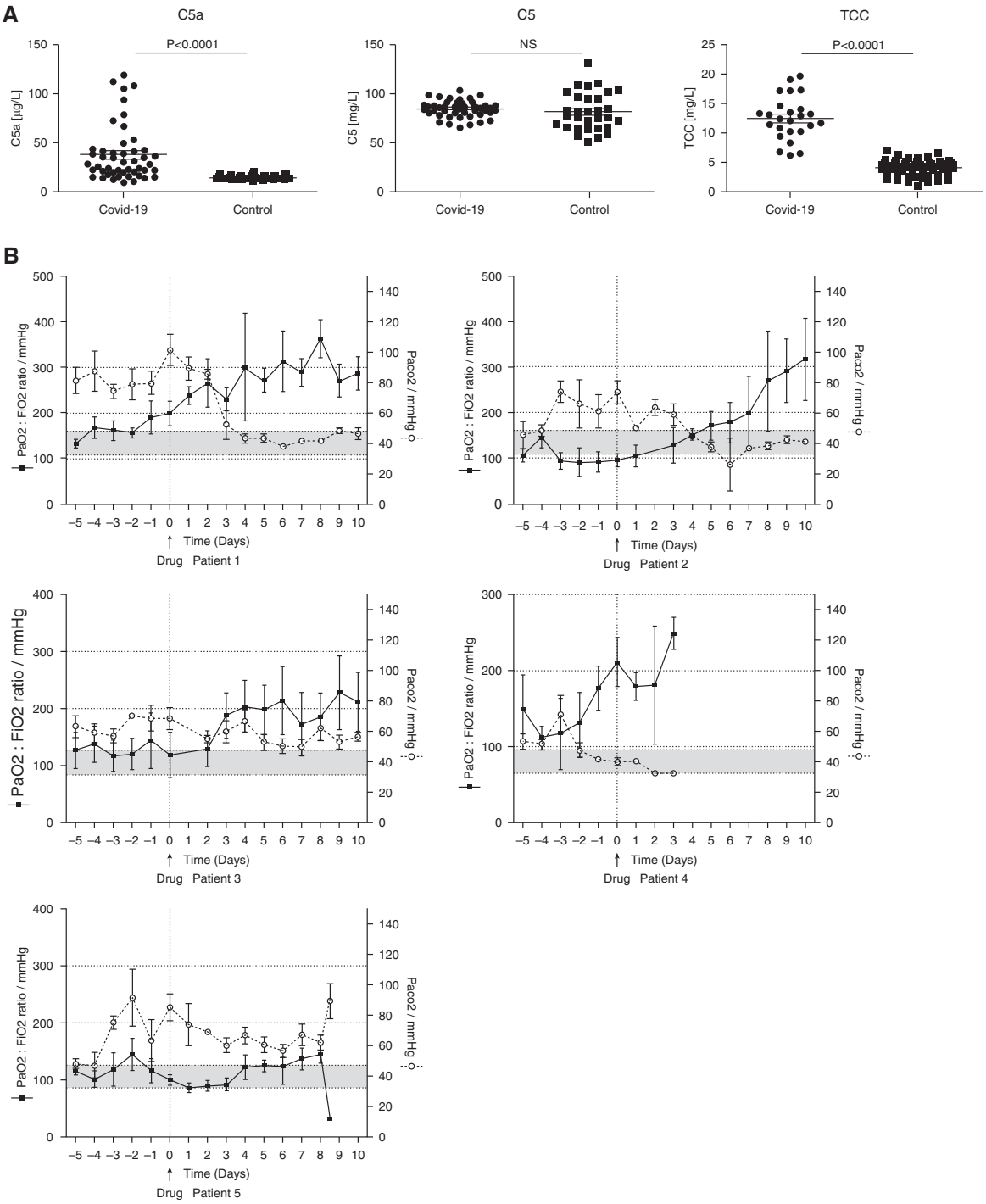

Figure 1. Complement activation in severe COVID-19 and response to C5 blockade. (*A*) Levels of terminal complement complex (TCC; in-house ELISA), C5a (Hycult ELISA), and C5 (in-house ELISA) were measured in ethylenediaminetetraacetic acid (EDTA) plasma from patients with severe COVID-19 and controls; TCC levels were significantly elevated compared with the healthy EDTA plasma controls (COVID-19, $n = 25$, mean = 12.5 mg/L; controls $n = 67$, mean = 4.1 mg/L; $P < 0.0001$, unpaired *t* test). C5a levels were also significantly elevated compared with healthy controls (COVID-19, $n = 25$, mean 43.0 µg/L; controls, $n = 32$, mean = 14.7 µg/L; $P < 0.0001$, unpaired *t* test). C5 levels were not different between COVID-19 ($n = 25$; mean = 84.5 g/L) and controls ($n = 31$, mean = 81.8 g/L; $P = 0.42$). Error bars are SE in each panel. Control samples were from a healthy adult donor EDTA plasma set that had previously been collected in the laboratory. (*B*) Serial trends in Pa_{O_2}:Fi_{O_2} ratio and Pa_{CO_2} were measured after LFG316 treatment. Plots represent the means ± 1 SD from arterial blood gas measures taken on the specified day from each of the five patients (labeled below) administered LFG316. Solid squares are Pa_{O_2}:Fi_{O_2} ratios; open circles are Pa_{CO_2} levels. Dotted lines indicate grading of acute respiratory distress syndrome (mild: 200–300 mm Hg; moderate: 100–200 mm Hg; or severe: <100 mm Hg); gray zone represents normal range for Pa_{CO_2}. Rapid clinical improvement in patient 4 leading to extubation on Day 3 after dosing obviated the requirement for additional measures. COVID-19 = coronavirus disease; NS = not significant.

Table 1. Demographic, Clinical, and Laboratory Parameters in the Treated Patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Demographics					
Sex	M	F	M	F	M
Age, yr	56	40	46	51	74
Past medical history	Esophagitis, psoriasis, allergic rhinitis, and hypogonadism	Type 2 diabetes, depression, posttraumatic stress disorder, and morbid obesity	Lambert Eaton syndrome, glaucoma, type 2 diabetes, and penile carcinoma *in situ*	Asthma	Hypertension; awaiting surgery for a benign posterior fossa tumor (on dexamethasone)
Prehospital symptomatic period, d	8	5	10	7	9
Time from hospital admission to LFG316 administration, d	34	7	22	12	11
Inpatient course, before LFG316	4 d of mechanical ventilation on ICU early in COVID-19 course before ward discharge for 14 d, then ICU readmission	Rapid escalation to critical care within 48 h of hospital admission	Rapid escalation to critical care within 12 h of hospital admission	Admitted to critical care Day 3 after hospital admission with severe respiratory failure	Admission to critical care 1 d after hospital admission with severe hypoxia
ICU course					
Predrug steroids, g*	3.75	0.3	0	0.45	0.48
Ventilation duration before LFG316, d	4 plus 12	5	22	9	11
High-frequency oscillatory ventilation	No	Yes	Yes	No	No
Nitric oxide	Yes	Yes	No	No	No
ECMO referral	No	Yes	No	No	No
Prone	Yes	Yes	Yes	Yes	Yes
Paralysis	Yes	Yes	Yes	Yes	Yes
Pulmonary emboli	Yes	No	No	No	Yes

		Patient 1			Patient 2			Patient 3			Patient 4			Patient 5		
	Normal Range	Before Dosing	First 48 h	Day 7–10	Before Dosing	First 48 h	Day 7–10	Before Dosing	First 48 h	Day 7–10	Before Dosing	First 48 h	Day 7–10	Before Dosing	First 48 h	Day 5–8
Hemoglobin, g/L	130–180	90.0	92.0	90.0	90.0	102	96.0	90.0	78.0	73.0	90	91.0	113	114	116	98.0
Platelets, $\times 10^9$/L	150–400	305	342	371	99	480	428	99	75	35	241	227	358	339	324	393
Neutrophils, $\times 10^9$/L	1.7–7.5	7.5	8.2	10.4	17.4	26.2	10.5	17.4	9.9	4.6	5.2	6.3	3.5	7.5	7.3	8.0
Lymphocytes, $\times 10^9$/L	1.0–4.5	1.5	1.1	1.6	0.9	3.0	1.4	0.9	0.4	0.1	1.0	1.2	1.7	1.3	1.0	1.9
Prothrombin time, s	9.0–13.0	13.0	11.7	—	12.3	13.0	13.0	11.4	—	12.1	12.9	12.6	—	13.0	12.5	13.5
Activated partial thromboplastin time, s	23.0–38.0	37.8	39.2	—	28.6	30.9	34.2	33.5	—	29.2	29.3	32.0	—	30.9	33.0	34.5
Fibrinogen, g/L	2.0–4.0	6.3	6.0	—	8.5	6.0	7.2	5.4	—	4.0	11.3	7.7	—	8.8	7.7	10.0
C3, g/L	0.75–1.65	2.13	1.86	2.03	1.80	1.67	1.93	1.12	1.17	1.22	1.54	1.73	2.02	1.49	1.36	2.00
C4, g/L	0.14–0.54	0.45	0.43	0.45	0.30	0.28	0.40	0.27	0.30	0.32	0.24	0.30	0.36	0.10	0.15	0.21
C5, mg/L	80.5–86.2	76.9	75.2	93.4	71.3	80.4	94.7	86.5	76.1	78.9	103.5	94.8	92.9	—	—	—
C5a, μg/L	8.8–22.3	119.1	28.6	16.8	36.1	22.1	15.6	28.0	16.8	18.6	31.4	22.0	26.5	—	—	—
Terminal complement complex, mg/L	1.2–7.2	17.3	6.5	3.3	13.1	3.2	8.6	10.3	3.8	5.3	11.3	5.5	12.9	12.4	2.1	7.6
Classical pathway hemolytic activity (CH50), hemolytic units	70–130	229.8	0	175.1	132.2	0	69.9	284.4	0	88.9	268.4	0	105.5	247.9	0	151.5
C-reactive protein, mg/L	<5	99	31	8	170	36	59	113	22	24	164	43	27	133	182	149
Ferritin, μg/L	15–300	666	599	354	350	266	169	3,004	—	384	473	248	—	424	421	508
Lactate dehydrogenase, U/L	125–200	478	329	469	500	533	370	571	—	287	306	241	—	313	315	326
Procalcitonin, μg/L	<0.05	0.14	0.08	0.05	0.57	0.27	0.20	3.27	3.09	1.01	0.08	0.05	—	1.32	0.48	0.66
Troponin I (high sensitivity), ng/L																
Male	0–34	23	13	12	—	—	—	89	—	46	—	—	—	9	20	44
Female	0–16	—	—	—	<2	<2	3	—	—	—	2	<2	—	—	—	—
Follow-up duration, days since admission (after LFG316)†	—		81 (48)			50 (43)			63 (42)			49 (38)			20 (8)	
Current care level‡	1–6		1			1			3			1			6	

Definition of abbreviations: COVID-19 = coronavirus disease; ECMO = extracorporeal membrane oxygenation.

*Steroids, total prednisolone equivalent dose given in the Critical Care Unit before administration of LFG316; in a comparator group of 28 clinically matched patients, steroid dose was 0.95 g (SD, 0.27 g).

†Correct at date of original submission, June 12, 2020; censored at Day 20 after admission for patient 5.

‡Care level at date of submission defined by six-point scale consisting of the following categories: 1 = not hospitalized; 2 = hospitalized, not requiring supplemental oxygen; 3 = hospitalized, requiring supplemental oxygen; 4 = hospitalized, requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both; 5 = hospitalized, requiring invasive mechanical ventilation, ECMO, or both; 6 = death.

COVID-19 lung pathology (5). We here report the contribution of complement activation and impact of complement blockade in severe COVID-19, defined as marked respiratory impairment requiring intensive care and ventilation support. Drugs were administered under the Novartis Managed Access Program and permission to undertake this case series study was granted by the director of research and development at Cardiff and Vale University Health Board.

Complement dysregulation was identified in critically ill patients with RT-PCR–confirmed COVID-19; terminal complement complex (TCC) and C5a levels were measured in mechanically ventilated patients in the Critical Care Unit at a single center if the clinician considered that the clinical trajectory was not improving (Figure 1A). Five patients were selected, based on high levels of TCC (above the mean + 2 SD for controls; 7.14 mg/L) and either treatment failure (patients 1–3) or failure to improve (patients 4 and 5) where death was not considered imminent (clinical judgement), for inclusion in a compassionate use study of complement blockade using LFG316 (tesidolumab; Novartis Managed Access Program), a C5-blocking monoclonal antibody (mAb) that prevents generation of the proinflammatory effectors C5a and membrane attack complex (6). As patients were unable to provide written informed consent, assent from relatives was obtained. Pretreatment disease course is summarized in Table 1. All five patients selected were paralyzed and proned while receiving mechanical ventilation. High-frequency oscillatory ventilation and nitric oxide were used alone or in combination in the first three patients. Duration of ventilation before LFG316 is shown in Table 1. Each patient received a single 1,500-mg dose of LFG316 by intravenous infusion, anticipated from unpublished Novartis data to fully inhibit C5 for >7 days, preceded by chlorpheniramine (4 mg) and hydrocortisone (100 mg). Antibiotic prophylaxis (phenoxymethylpenicillin or clarithromycin) was provided to mitigate risk of encapsulated bacterial infections. In all patients, CH50 was completely suppressed up to Day 4 after treatment with partial recovery at Day 7; TCC and C5a levels fell to within the normal range and remained low through Day 7; CRP (C-reactive protein) levels were elevated before dosing and, except for patient 5, fell after dosing (>80%) and remained reduced through Day 7 (Table 1). Patients 1, 2, and 4 showed rapid resolution of CRP and improved oxygenation and CO_2; recovery in patient 3 was much slower, but all four showed improved ventilation after dosing (Figure 1B). Patient 5 failed to respond to LFG316 despite complete complement blockade, developed a sudden pulseless electrical activity cardiac arrest, and died 9 days after treatment; uniquely, CRP levels did not fall after treatment in this patient, suggesting that there was another driver of inflammation, likely the identified occult *Klebsiella* infection. Among our severe COVID-19 cohort who did not receive LFG316, 67 of 71 were mechanically ventilated and paralyzed, and 28 of these were proned. Mean duration of ventilation in this subgroup was 19.5 days. Death occurred in 13 (46.4%).

Currently, there are no proven effective therapies for critically ill patients with COVID-19 requiring mechanical ventilation (7). The potential efficacy of anticomplement drug therapy in COVID-19 has been tested in a handful of patients to date and was recently reviewed (8). Diurno and colleagues treated four patients with COVID-19 with the C5-blocking mAb eculizumab, weekly ×4 (9). All were self-ventilating with moderately elevated CRP that fell after treatment; all recovered over 14 days. Mastaglio and colleagues treated a single nonventilated patient with the C3 blocker AMY-101 continuously infused over 14 days with favorable outcome (10). In each of these reports, patients selected had relatively mild disease and no measurements of complement parameters to assess dysregulation before or in response to drug were reported.

We describe a preliminary evaluation of the potential benefit of C5 blockade in severe COVID-19; we show that the C5-blocking mAb LFG316 could be administered in critically ill mechanically ventilated patients with COVID-19; a single dose of LFG316 blocked C5 activity and complement activation for at least 4 days in all treated patients. In four of five patients, there was sustained improvement in clinical state persisting beyond C5 blockade. Four days after dosing, an occult *Klebsiella* infection was found in the nonresponding patient 5; given the known impact of complement blockade on risk of infection with gram-negative bacteria, it is possible that LFG316 treatment exacerbated the infection. No other adverse effects of therapy were seen in any of the treated patients. Our results suggest that transient blockade of C5 is sufficient to interrupt the hyperinflammatory cycle in severe COVID-19 and permit recovery even in the most extreme clinical situations. This finding differs from previous case reports of complement inhibition in COVID-19 where patients were less severely ill and treated for extended periods (8–10). Our data are supportive of ongoing clinical trials of C5 blockade in severe COVID-19 and may inform design of current and future trials of anticomplement drugs where repeated or prolonged complement blockade are proposed; indeed, prolonged complement blockade may not only be unnecessary for patient benefit but also be harmful by increasing infection risk, a known consequence of complement blockade, over weeks or months in recovering patients, likely on other immune suppressants and with residual lung damage.

Study limitations include small cohort size and lack of a randomized control group. Although our data identify complement dysregulation and support clinical benefit of complement blockade in severe COVID-19, these limitations make it impossible to demonstrate proof of efficacy. Further studies are warranted to confirm impact of complement blockade on hyperinflammatory and/or thrombotic components of COVID-19 disease and to establish optimal timing and dosing. ■

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The Effect of Hypopnea Scoring on the Arousal Threshold in Patients with Obstructive Sleep Apnea

A low respiratory arousal threshold ($ArTH_{Resp}$) is one of several endotypes that contribute to the pathogenesis of obstructive sleep apnea (OSA). Accordingly, it has emerged as a potential "drug-able" target to treat OSA (1). Notably, Edwards and colleagues (2) developed a clinical screening tool to identify OSA patients with low $ArTH_{Resp}$ based on three predictive variables obtained from standard overnight sleep studies (i.e., polysomnograms [PSGs]): *1*) nadir oxygen saturation $>$82.5%, *2*) apnea–hypopnea index (AHI) $<$30 events/hour, and *3*) percentage of respiratory events that are hypopneas (%hypopnea) $>$58.3% that correctly predicted the presence of a low $ArTH_{Resp}$ in 84% of patients.

However, a key limitation of this tool is that it was developed using hypopnea scoring rules from the older "Chicago" ($AASM_{1999}$) criteria (3), which have since been updated to the current American Academy of Sleep Medicine (AASM) "Recommended" ($AASM_{2012Rec}$) and "Acceptable" ($AASM_{2012Acc}$) criteria. The $AASM_{2012Rec}$-defined hypopneas are associated with a $\geqslant$3% oxygen desaturation or EEG arousal, whereas $AASM_{2012Acc}$ requires a stricter $\geqslant$4% oxygen desaturation and does not consider arousals (4). Though it is established that differing scoring criteria impact the AHI and %hypopnea (5–7), we recently demonstrated that scoring criteria also influence the measurement of another key OSA endotype (8), the sensitivity of the ventilatory control system. However, the extent to which changes in scoring criteria impact the predictive utility of the $ArTH_{Resp}$ score is unknown. Accordingly, we aimed to determine the influence that the 2012 scoring criteria has on the tool's performance.

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