reflected the severity of the pretransplant condition as well as further decondition while receiving ECMO. Therefore, understandably, transplant clinicians tend to reserve scarce lung resources to those not on ECMO. Furthermore, there are considerable concerns of theoretical recurrence of ILD in the transplanted lungs secondary to the underlying connective tissue disease. However, in our case series, ECMO bridging to lung transplant was the only life-saving intervention for those who further deteriorate from hypoxia despite maximal immunosuppression and mechanical ventilation support. It is important for clinicians to be aware of ECMO as a modality to bridge to lung transplant as it is not available in many centres globally. In three of the four patients, we have long-term data confirming no recurrent lung disease after lung transplant. This is the largest case series demonstrating successful lung transplant can be achieved in patients with RP-ILD secondary to anti-MDA5 DM requiring ECMO for oxygenation.

Based on our local experience, we recommend consulting a transplant team early for assessment. Following transplant, maintenance therapy with glucocorticoid, mycophenolate and tacrolimus, for both transplant anti-rejection and autoimmune ILD, seems appropriate.

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Kun Huang [1], Robert D. Levy[2] and J. Antonio Avina-Zubieta[1,3]

[1]*Division of Rheumatology, University of British Columbia,* [2]*Division of Respirology, University of British Columbia and* [3]*Arthritis Research Canada, University of British Columbia, Vancouver, BC, Canada*

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Correspondence to: Kun Huang, Division of Rheumatology, University of British Columbia, 706-13737 96 Ave, Surrey, BC, Canada. E-mail: khuang@cmmt.ubc.ca

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Real-life experience of tocilizumab use in COVID-19 patients

Rheumatology key message

- The current preliminary evidence of use of tocilizumab in COVID-19 patients is promising.

Dear Editor, Coronavirus disease 2019 (COVID-19) has been confirmed in 2 878 196 people worldwide with case fatality rate 6.9% as per WHO Situation Report of 27 April 2020. Accumulating evidence suggests that a subgroup of patients with COVID-19 might have a hyper- inflammation (aka cytokine storm syndrome) evidenced by elevated circulating levels of several cytokines including IL-6. Tocilizumab, an anti-IL-6 receptor antibody used for rheumatoid arthritis and temporal arteritis and approved by the FDA for cytokine release syndrome, has been used in many countries as an experimental treatment for these patients.

Our objective was to summarize the current evidence of tocilizumab use in COVID-19 patients. We searched Medline, Embase, Cochrane Database of Systematic

Table 1 Outcome measures, laboratory parameters and adverse events after tocilizumab treatment

Author, year	Study type	Country	Sample size, *n*	When Improvement noticed	CRP (mg/l)	Progress	Adverse events
Cellina, 2020	Case report	Italy	1	Improvement in his blood tests 1 day after	96mg/l 1 day after administration	Clinical condition progressively improved and ventilatory support was gradually weaned	Not reported
De Luna, 2020	Case report	France	1	SpO2 at 97% with oxygen at a rate of 3 l/min and no fever 1 day after	Not reported	Discharge 3 days after tocilizumab	Not reported
Di Giambenedetto, 2020	Case series	Italy	1	Not reported	Normal levels 6 days after	PaO2/FiO2 ratio improved at 210 7 days after and fever resolved 3 days after	No adverse events
			1	Not reported	13mg/l 4 days after	Clinical condition improved with resolution of fever after 48 hours	
			1	Not reported	92mg/l 2 days after and normal levels 10 days after	Progressive resolution of dyspnoea and oxygen saturation at 98% with FiO2 0.31 6 days after	
Ferrey, 2020	Case report	USA	1	Vasopressor requirement and PaO2/FiO2 ratio remain variable	Not reported	Vasopressor requirement and PaO2/FiO2 ratio remain variable	Not reported
Fontana, 2020	Case report	Italy	1	Apyrexial since tocilizumab administration	Not reported	PaO2 showed progressive improvement and oxygen treatment was stopped. Discharge on day 22 after admission with SO2 95% on room air	Suspected leukopoenia with neutropenia resolved with IVIG, urinary culture positive for multi-resistant *Pseudomonas aeruginosa* treated with meropenem
Luo, 2020	Retrospective study (27 January to 5 March 2020)	China	15	Not reported	Normal levels by day 7 in patients with clinical improvement or stabilization	Eight patients (53.3%) clinical stabilization, 2 (13.3%) clinical improvement, 3 (20%) died (critically ill patients), 2 (13.3%) disease aggravation (one critically and other seriously ill)	Not reported
Michot, 2020	Case report	France	1	Rapidly afebrile	33mg/l 4 days after	Clinical improvement and oxygen was fully discontinued on day 7 of admission, patient ultimately clinically fully recovered	No
Morrison, 2020	Case series	USA	1	Not reported	Not reported	Not reported	One day after: serum triglyceride (TG) levels at 1196 mg/dL, amylase 309 IU/l and lipase104 IU/l, TG decreased to over 200 in one day and remained stable until day 17
			1	Not reported	Not reported	Not reported	3 days after TG levels at 1436 mg/dL with normal amylase and lipase
Pereira, 2020	Retrospective study (13 March to 4 April 2020)	USA	14	Not reported	Not reported	Three patients (21.4%) died, 4 (28.6%) remain in ICU, 5 (35.7%) remain with moderate disease on the general medical floor and 2 (14.3%) have been discharged	No adverse events
Roumier, 2020	Retrospective study (21 March to 2 April 2020), median follow-up: 8 days	France	30	Not reported	Not reported	Three patients (10%) had died, while 4/7 (57.1%) and 6/30 (20%) were discharged from the ICU and from hospital respectively	2 patients (6.7%) developed mild hepatic cytolysis and one patient (3.3%) ventilator-acquired pneumonia
Xu, 2020	Retrospective study (5 to 14 February 2020)	China	21	Apyrexial on the first day after tocilizumab and remained stable after	Normal values in 16 patients (84.2%) 5 days after	Nineteen patients (90.5%) have been discharged including two critical patients and the rest remained under hospital observation with remarkable clinical improvement and no fever. The mean hospitalization time was 13.5 days after the treatment	No adverse events
Zhang, 2020	Case report	China	1	Not reported	Normal levels 2 weeks after	Chest tightness disappeared in 3 days, discharge 19 days after	Not reported
Schleicher, 2020	Case report	South Africa	1	Improvement in his fever, biomarkers and hypoxaemia within 24 hours	Normal levels 7 days after	Discharged 3 days after	Not reported

Reviews, the reference lists of relevant articles, the preprint servers medRxiv and ChinaXiv and the ResearchGate website. The last search was carried out on 25 April 2020. We included all original studies, including case reports, in human adult patients (aged >18) with confirmed COVID-19 treated with tocilizumab regardless of publication status.

Our researches yielded a total of 13 eligible articles ($n = 92$ patients), four retrospective studies [1–4], two case series [5, 6] and seven case reports [7–13]. Three articles were from China [1, 4, 12], France [3, 8, 13], Italy [5, 7, 10] and the USA [2, 6, 9], respectively and one from South Africa [11] with the largest one from France ($n = 30$ patients) [3]. A total of 66 (72%) of the patients were male. The median age was 58.8 years (interquartile range, 56.8–61 years). There was a broad range of comorbidities, including hypertension and diabetes, and 20/92 (21.7%) patients were on immunosuppression [2, 3, 10, 12].

The main indication of tocilizumab use was worsening hypoxia. CRP was 189 mg/l (interquartile range, 126–189 mg/l) and based on 41 patients, IL6 levels were 132.4 pg/ml (interquartile range, 46.8–132.4 pg/ml). Median ferritin levels were 2,682 ng/ml based on 32 patients. The imaging (chest X-ray or CT chest) before tocilizumab initiation demonstrated worsening findings including ground-glass opacities in comparison with the one on admission [4, 9, 11]. Tocilizumab was commenced from day 8–22 from the onset of symptoms and the majority of patients (42.4%) had one dose of 8 mg/kg or 400 mg intravenously. Patients also received other experimental treatments, such as antiviral therapy [4–6, 11–13] and hydroxychloroquine [3, 5, 6, 8–10]. Thirty-one (34%) patients also received methylprednisolone [1, 4, 10, 12].

Outcome measures, laboratory parameters and adverse events after tocilizumab treatment are presented in Table 1. The patient progress results are available for 76 out of 92 patients. A total of 44/76 (57.9%) patients improved and 31/76 (40.8%) were discharged from the hospital. Furthermore, 13/76 (17.1%) patients remained stable or with moderate disease. Nine out of 76 (11.8%) patients died, eight (10.5%) patients remain in critical condition [2, 3, 9] and two (2.6%) patients got worse. Initial improvement was noticed in 25/76 (32.9%) patients within the first 24 h with reduction or even normalization of temperature [4, 7, 8, 10, 11]. CRP decreased in accordance with the clinical improvement and even normalized after a median of 5 days [1, 4, 5, 11, 12]. Based on the IL-6 levels of 17/92 (18.5%) patients, IL-6 spiked shortly after the tocilizumab administration and then decreased, but continued to increase in four patients that died or deteriorated [1, 10, 12]. The temporary increase in IL-6 serum levels is probably explained by the unavailability of IL-6 receptor which is blocked by the tocilizumab. A total of 3/44 (6.8%) patients with clinical improvement also had repeat CT chest that demonstrated reduction in ground-glass opacities [7, 12, 13]. Tocilizumab was well tolerated, except for six (6.5%) patients [3, 6, 10].

The results are encouraging (75% improved, remained stable or with moderate disease with Tocilizumab), but should be evaluated with caution due to the low quality of studies (retrospective nature, small sample size, missing data, no clear outcome measures). Future studies should focus on patient-centred outcome measures, such as death and prevention of ventilation. Randomization should also be considered in any future work. Additionally, the above positive findings could be misleading because of publication bias and the under-reporting of negative studies. However, this preliminary evidence supports the consideration of tocilizumab in the research efforts in the fight against the COVID-19 hyper-inflammation response.

In line with the above findings, on 27 April, the results of a French open-label randomized controlled trial ($n = 129$) were announced by the Assistance Publique-Hôpitaux de Paris. A total of 129 patients with COVID-19, not requiring intensive care upon admission, were randomized equally to standard of care with tocilizumab and standard of care alone. According to the press release, a significantly lower proportion of patients reached the primary outcome (need for ventilation or death at day 14) in the tocilizumab arm. Results of this study will be submitted for publication in a peer-reviewed journal. There are still 32 ongoing clinical and observational trials registered on clinicaltrials.gov (accessed on 29 April 2020). However, these studies vary in participant and intervention criteria with several diverse primary and secondary outcomes. This may make future attempts of synthesizing the results across clinical trials difficult, leading to different policies in different countries. This heterogeneity highlights the global need to identify which is the right time and dosing scheme of tocilizumab for patients with COVID-19.

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Anastasia-Vasiliki Madenidou [1] **and Marwan Bukhari** [1]

[1]*Rheumatology Department, University Hospitals of Morecambe Bay NHS Foundation Trust, Barrow-in-Furness, Lancaster, UK*

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Correspondence to: Marwan Bukhari, Rheumatology Department, University Hospitals of Morecambe Bay NHS Foundation Trust, Royal Lancaster Infirmary, Ashton Road, Lancaster LA1 4RP, UK.
E-mail: marwan.bukhari@mbht.nhs.uk

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Novel use of burosumab in refractory iron-induced FGF23-mediated hypophosphataemic osteomalacia

Rheumatology key message

- Burosumab ought to be considered in the management of iron-induced FGF23-mediated hypophosphataemic osteomalacia.

Dear Editor, Refractory iron-induced fibroblast growth factor 23 (FGF23) mediated hypophosphataemic osteomalacia is an uncommon complication of parenteral iron therapy. Treatment thus far in case reports has consisted of iron cessation and phosphate substitution [1–4]. To our knowledge, we describe the first reported use of burosumab therapy for this condition.

We present a 32-year-old man with severe Crohn's disease and iron-deficiency anaemia. Computed tomography angiography revealed focal ileocolic venous portal hypertension with recurrent lower intestinal blood loss. A transjugular intrahepatic portosystemic shunt was not considered feasible and regular infusions of 250 mg ferric carboxymaltose fortnightly were instituted over oral therapy, given the extensive gastrointestinal disease.

After one year, the patient developed severe foot and leg pain and was diagnosed with multiple insufficiency metatarsal and tarsal fractures. Laboratory workup revealed profound hypophosphataemia (0.38 mmol/l), elevated FGF23 (320 RU/ml) and no pathogenic variants in PHEX, ENPP1, SLC34A3, DMP1 or KLOTHO. He was started on Sandoz phosphate, alfacalcidol and was switched from ferric carboxymaltose to iron isomaltoside. There was no appreciable clinical benefit and tolerability to oral phosphate supplementation was poor, owing to an increase in diarrhoea.

One year later, he developed progressive severe left hip pain after minor trauma. MRI demonstrated a femoral pseudofracture. He was switched to central intravenous phosphate replacement for ten hours a day, five days a week with partial weight bearing. Follow-up MRI three months later demonstrated a complete left femoral fracture, new right femoral pseudofracture and multiple pelvic fractures (Fig. 1A).

Given the progression of his bone disease and likely need for bilateral hip arthroplasty, the patient was started on burosumab (0.3 mg/kg) subcutaneously every four weeks. After the first dose, he reported a significant resolution of symptoms mirrored with improvements in laboratory measures. Serum phosphate levels improved from 0.38 mmol/l to 1 mmol/l and alkaline phosphatase levels reduced from 218 IU/l to 175 IU/l. Furthermore, subsequent MRI showed complete resolution of the right femoral head fracture and near complete healing of the left femoral and pelvic fractures (Fig. 1B).