Background: The cytokine storm syndrome (CSS) associated with COVID-19 pneumonia occurs in up to 20% of the admitted patients causing high morbidity and mortality [1]. In the COVID High-intensity Immunosuppression in Cytokine storm syndrome (CHIC) study [1] we reported that CSS patients, who despite high-dose methylprednisolone (MP) treatment still showed severe respiratory deterioration, received subsequent single dose tocilizumab (TCZ) treatment. Our clinical experience with TCZ, every 4 weeks in RA, where a pre-dose serum concentration of > 1 µg/ml is sufficient to block all interleukin (IL)-6 receptors and thereby induce and maintain clinical remission, prompted further investigation of TCZ pharmacokinetics in patients with COVID-19 CSS [1,2].

Objectives: In this pharmacokinetic study we investigated the clinical-pharmacokinetic rationale for a single TCZ dose in a subset of COVID19 induced CSS patients.

Methods: Patients with COVID-19-associated CSS, defined as rapid respiratory deterioration plus at least two biomarker elevations (C-reactive protein (CRP) >100 mg/L; ferritin >900 µg/L; D-dimers >1500 µg/L), received per protocol high-dose intravenous MP for 5 consecutive days. If the respiratory condition had not improved sufficiently, TCZ (8 mg/kg, max. 800 mg) single infusion was added on or after day 2[1]. TCZ serum samples were drawn at TCZ day 1, 3 and 10 to assess TCZ serum concentrations with a validated ELISA-method. A nonlinear-mixed effects model was developed based on all concentration time data to characterise TCZ pharmacokinetics (NONMEM). Subsequently individual pharmacokinetic parameters (AUC0-inf, Cmax, time above 1 µg/ml) were estimated and TCZ concentration-time observations were plotted against the individual predicted concentrations to visualize the complete TCZ concentration-time curve.

Results: In total, 34 patients with COVID19 induced CSS still showing clinical deterioration upon MP treatment received TCZ per protocol [mean (SD) age: 62 (12) years, 22% female, baseline mean (SD) bodyweight: 87 (17) kg, CRP: 108 (833) mmol/L, ferritin: 1653 (911) µg/L, D-dimers 4462 (7272) µg/L]. TCZ clearance was described by a homogeneous population-kinetics model yielding 87 serum samples. TCZ serum concentrations followed a biphasic course [Distribution volume 5.0 L (3.3-7.3), Area Under the Curve$_{0-\infty}$ 1st dose (682 (397-913) mg/L*days), Cmax 137 mg/L (88 – 199), half-life (linear) 3.5 days (2.3-4.1)]. In all patients, TCZ serum concentrations remained above the theoretical maximum IL-6 receptor occupancy concentration of 1 µg/ml for at least 12 days, depicted in Figure 1.

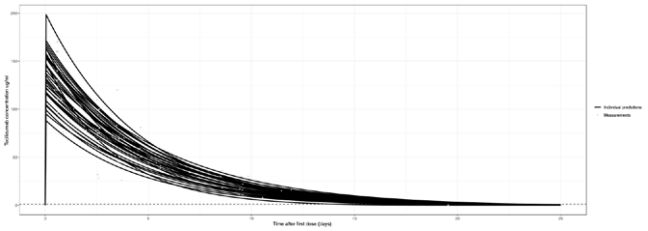

Figure 1. Predicted concentration-time profiles after single dose tocilizumab in 34 methylprednisolone pretreated patients with COVID-19 induced cytokine storm syndrome. Dashed line: maximum IL-6 receptor occupancy concentration 1 µg/ml

Conclusion: Based on our study results on the pharmacokinetics of TCZ in patients with severe COVID-19 induced CSS we conclude that the clearance of TCZ is faster compared to RA-patients at steady state. However, our observations indicate that a single dose of tocilizumab in CSS-patients is enough to cover IL-6 mediated hyperinflammation. Restricting TCZ to a single dosage can prevent overtreatment, drug shortage and saves costs, while still maintaining efficacy, as most patients will have overcome their hyperinflammatory period of the CSS after 10-14 days.

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POS1257

HYPOGAMMAGLOBULINEMIA IS A SIGNIFICANT RISK FACTOR FOR MORTALITY IN PATIENTS WITH ANCA ASSOCIATED VASCULITIS AND COVID-19

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Background: The negative impact of COVID-19 in patients with ANCA associated vasculitis (AAV) and patients on rituximab (RTX) treatment have been reported (1). Risk factors for severe course of COVID-19 and increased mortality in these patients are unclear.

Objectives: To evaluate the course of COVID-19 in our AAV cohort and identifying risk factors for mortality.

Methods: Patients with AAV who were classified according to CHCC and whose scheduled last visit were after December 2019 were screened and evaluated for COVID-19 either by phone call or in the clinic. Records of patients with a history of hospital admission due to COVID-19 were evaluated. Cumulative clinical findings and treatment history were noted. Hypogammaglobulinemia (hIgG) was defined as IgG level below 700 mg/dl. All inpatients with a diagnosis of COVID-19 were screened for hIgG and IVIG was administered if necessary.

Results: Eighty-nine patients (47.2% female, mean age 56 + 12.5 (28-81)) were included into the study. The diagnosis was GPA in 56 (62.9%) and MPA in 33 (37.1%) patients. Mean follow up time was 91 + 53.4 (26-272) months. Anti-PR3 and anti-MPO were positive in 46 (51.7%) and 32 (35.9%) patients, respectively. Lower respiratory tract (LRT) involvement was present in 72 (80.9%) and 10 patients had a history of diffuse alveolar haemorrhage (DAH). Sixty-one patients (68.2%) had a history of rapidly progressive glomerulonephritis (RPGN) and 21 (23.6%) had peripheral nervous system (PNS) involvement.

Fifteen (16.9%) patients had COVID-19; 14 of them were PCR positive, one patient had symptoms and thorax CT findings compatible with COVID-19. Pulmonary infiltrates were observed in 13 patients (86.7%); 9 (60%) had severe pneumonia. Twelve patients (85.7%) were hospitalized, 6 patients (42.9%) needed ICU admission and 5 patients (35.7%) died. Tocilizumab and anakinra for hyperinflammation during COVID-19 were used in 1 (6.7%) and 4 (26.7%) patients, respectively.

Four out of five deceased patients (3 on RTX treatment, 1 with renal transplant) were in remission at the time of COVID-19. COVID-19 was detected in a patient with disease flare and DAH, during treatment with high dose steroids and plasmapheresis. hIgG was detected in all deceased patients from COVID-19 during hospital admission (mean IgG: 495±113.2 mg/dL).

Table 1. Comparison of risk factors for CI and mortality in patients with AAV

	COVID-19 (n=15)	Non-infected (n=74)	p	OR	Death (n=5)	Survive (n=10)	p2	OR2
Age	53.4±11.9	56.6±12.6	NS		51.2±12.6	54.6±12.1	NS	
Sex (female)	6	35	NS		4	2	0.036	14 (0.9-207)
LRT Involvement	14	58	NS		5	9	NS	
DAH	4	6	0.038	4.1 (1-16.9)	1	3	NS	
RPGN	15	46	0.004	8.5 (1-68.4)	5	7	NS	
PNS involvement	3	18	NS		3	0	0.005	9 (1.4 - 57)
RTX treatment	10	33	NS		3	7	NS	
hIgG in outpatient visits	6	7	0.02	6.3 (1.8-23.3)	4	2	0.02	16 (1.5-234)
hIgG during hospitalization due to CI	-	-	-	-	5	4	0.025	2.5 (1.2-5.4)
Flares≥1	7	25	NS		4	3	NS	
Chronic Renal Insufficiency	7	22	NS		4	3	NS	

Symptomatic COVID-19 was more frequent in patients with a history of DAH, RPGN and hIgG. hIgG during the follow-up was significantly associated with COVID-19 in multivariable analysis (p=0.01, OR=20,6 %95 CI (2-210). Comparison of patients who died of COVID-19 and survived showed that female sex, PNS involvement and hIgG during the clinical course and hospital admission were risk factors for increased mortality (Table 1). Age, smoking, treatments, history of flares or serious infections, remission status and chronic renal insufficiency did not differ between groups.

Conclusion: The frequency and mortality from COVID-19 is found to be high in our AAV cohort compared to previous reports (1). Patients with serious lung or renal involvement are prone to symptomatic COVID-19. Previously reported severe outcomes on RTX therapy might be related to consequent hIgG. High dose IVIG treatment may not be sufficient in improving survival in AAV patients with severe COVID-19 and hIgG.

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POS1258 MISSING THE WINDOW OF OPPORTUNITY: EARLY ARTHRITIS CLINICS IN TIMES OF COVID-19

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Background: The outcomes of patients with chronic inflammatory arthritis (IA), such as rheumatoid arthritis (RA), have dramatically improved over the past 20 years. Earlier identification of IA and prompter treatment institution have been key advancements, promoted by the constitution of Early Arthritis Clinics (EAC) and the development of more sensitive classification criteria for RA. The outbreak of new COronaVIrus Disease 2019 (COVID-19) has quickly become a global health emergency and has forced a rearrangement in the management of other non-COVID-19 diseases. The impact of the lock-down of the healthcare systems on chronic inflammatory diseases such as RA is expected to be significant but is at present unknown.

Objectives: To assess the effects of the lock-down imposed by the COVID-19 pandemic on the referral and clinical presentation of patients with new-onset RA.

Methods: Data were retrieved from the Pavia EAC inception cohort, established in 2005 for the early identification of patients with new-onset IA. Referral criteria to the EAC include: ≥3 swollen joints (SJ) and/or <3 SJ and positive squeeze test and/or <3 SJ and morning stiffness >30 min. Demographic and clinical characteristics of the patients are assessed at baseline and regularly over follow-up. At 31 Dec 2020, the Pavia EAC collects information on 2.508 patients. For this study, baseline characteristics of the patients referred in the semester following the COVID-19 lock-down (Jul-Dec 2020) were compared with: (i) patients referred in the semester immediately preceding the lock-down (Jul-Dec 2019); (ii) patients referred in the semester following the publication of the 2010 RA classification criteria (Jan-Jun 2011); (iii) patients referred in the semester preceding the publication of the 2010 criteria (Jul-Dec 2009).

Results: In the semester following the lock-down imposed by the COVID-19 pandemic, there was a decrease in the referral of patients with new-onset suspected IA compared with previous periods (n=71 vs n=91 in the semester before the lock-down, n=96 in the first semester of 2011, n=101 in the second semester of 2009). Furthermore, fewer of the referred patients fulfilled RA criteria at presentation (36.6% vs 44.3%, 46.5% and 42.9% in the other semesters). Among patients with RA, more were autoantibody-positive (72% vs 50%, 49.1% and 52.2%). There was a trend for increased diagnostic delay in the overall cohort of RA after the COVID-19 lock-down (Figure 1A). The delay was particularly longer in autoantibody-positive patients, returning to the values seen before the introduction of the 2010 RA criteria (Figure 1B). In contrast, the few autoantibody-negative patients were referred earlier (Figure 1C). Disease activity at presentation was significantly higher in RA patients presenting after the lock-down compared with the progressive trend for reduction observed over the previous years, irrespective of the autoantibody status (Figure 1D-F). Such increase was determined by an inversion of the trend towards lower levels of objective parameters of inflammation, such as the swollen joint count (Figure 1G-I) and acute phase reactants, and a further increase in the secular trend towards worsening of patient-derived measures, such as the tender joint count and patient global assessment (Figure 1J-L).

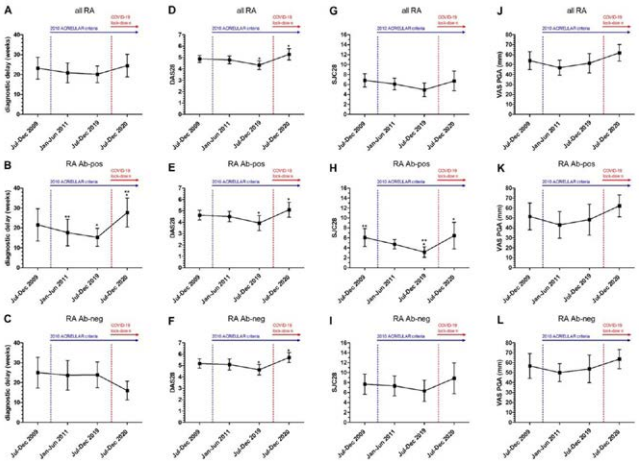

Figure 1. Effects of COVID-19 lock-down on new-onset RA at presentation.

Conclusion: The COVID-19 pandemic is posing unprecedented challenges in the management of patients suffering from chronic diseases. RA has returned to be diagnosed outside the window of opportunity, with a significantly higher inflammatory burden at presentation. The many benefits of early diagnosis, which have dramatically changed the outcomes of autoantibody-positive RA, are at risk of vanishing in short times. Equally important, autoantibody-negative RA is at risk of further under-diagnosis and under-treatment.

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POS1259 FAVOURABLE SHORT-TERM COURSE OF COVID-19 IN PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER USING BIOLOGIC AGENTS

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Background: COVID-19 runs a variable course resulting in acute respiratory distress syndrome and death in a subset of patients. The entry of SARS-CoV-2 into the cell stimulates innate immunity including NLRP3 inflammasome and lead to development of adaptive immunity later. Hyperinflammatory response with the release of proinflammatory cytokines including IL-1β and IL-6 results in cytokine storm in some patients with a worse outcome. Colchicine acts on NLRP3 inflammasome and inhibits and IL-1 mediated inflammatory attacks in gout and familial Mediterranean fever (FMF) patients. Patients with inadequate response to colchicine may benefit from anti-IL-1 biologic agents such as anakinra and canakinumab. Recently, favourable effects of anakinra have been observed in COVID-19 patients with findings of cytokine storm.

Objectives: We aimed to evaluate the impact of COVID-19 among refractory FMF patients followed-up in tertiary referral with the treatment of biologic agents and also document the course of COVID-19 in these patients.

Methods: We searched out database of FMF patients to identify those using biologic agents (anti-IL-1, anti-IL-6 or anti-TNF) for colchicine-refractory FMF. We interviewed the patients using a standard questionnaire by phone call for symptomatic COVID-19 and evaluated those patients who described findings of COVID-19 further by their hospital records or inviting them to the hospital for additional investigations.

Results: We identified 183 patients and contacted 106 of them by phone in May-October 2020. A history of symptomatic COVID-19 was documented in 7 FMF patients who were on a biologic agent. Six were on anti-IL-1 and one was on anti-TNF, and one of the patients was not taking his biologic agents for 1 year. All of 7 patients had a favourable outcome. All but 1 patient followed at home and none of them developed findings of cytokine storm, thromboembolism and secondary bacterial infection. Hospitalized patient did not require intensive care unit (ICU) support or mechanical ventilation, and he was not given additional anti-inflammatory medications.