Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Association between tocilizumab treatment of hyperinflammatory patients with COVID-19 in a critical care setting and elevated incidence of hospital-acquired bacterial and invasive fungal infections

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SUMMARY

Background: Tocilizumab is an interleukin-6 inhibitor that reduces mortality and the need for invasive mechanical ventilation, while increasing the possibility of successful hospital discharge for hyperinflammatory patients with severe coronavirus disease 2019 (COVID-19). No increase in adverse events or serious infections has been reported previously.
Aim: To describe the characteristics and outcomes of patients with severe COVID-19 in critical care who received tocilizumab, and to compare mortality and length of hospital stay for patients who received tocilizumab (N=41) with those who did not (N=33).
Methods: Retrospective review of data related to patients with COVID-19 who received tocilizumab in a critical care setting from 1st January to 31st December 2021.
Findings: Amongst COVID-19 survivors, those who had received tocilizumab had longer intensive care unit (ICU) stays (median length 21 vs 9 days) and hospital stays (45 vs 34 days) compared with those who had not received tocilizumab. Thirty-day mortality (29% vs 36%; P=0.5196) and 60-day mortality (37% and 42%; P=0.6138) were not significantly lower in patients who received tocilizumab. Serious bacterial and fungal infections occurred at higher frequency amongst patients who received tocilizumab [odds ratio (OR) 2.67, 95% confidence interval (CI) 1.04–6.86; P=0.042], and at significantly higher frequency than in non-COVID-19 ICU admissions (OR 5.26, 95% CI 3.08–9.00; P<0.0001).
Conclusions: In this single-centre study, patients in critical care with severe COVID-19 who received tocilizumab had a greater number of serious bacterial and fungal infections, but this may not have been a direct effect of tocilizumab treatment.

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Introduction

On 20th February 2020, coronavirus disease 2019 (COVID-19) was added to the existing list of notifiable diseases in the Republic of Ireland [1], with the first case of the disease diagnosed less than 10 days later on 29th February 2020 [2]. To date, the epidemiology of COVID-19 in Ireland has been characterized by five waves of infection, with onsets in March 2020, August 2020, November 2020, June 2021 and December 2021 [3].

The third wave of COVID-19 in Ireland began in late November 2020, and peaked during the first week of January 2021. In that week alone, 45,726 cases were diagnosed nationally, with County Limerick reporting 2470 cases (5.4% of the national total), equating to an incidence of 1267.3 per 100,000 population, the fourth highest incidence of the disease in the country at that time [4].

In January 2021, the Health Service Executive published interim guidance on the use of tocilizumab in the management of hospitalized patients with severe COVID-19 [5]. Tocilizumab is a humanized monoclonal antibody against the interleukin-6 (IL-6) receptor. Tocilizumab inhibits the binding of IL-6 to membrane and soluble IL-6 receptors, blocking IL-6 signalling and thus reducing inflammation [5]. Its use was to be considered, after multi-disciplinary team (MDT) discussion, for patients demonstrating an inadequate response to systemic corticosteroids, and who either: (i) required intensive care unit (ICU) admission with severe pneumonia necessitating organ support; or (ii) were non-ICU patients with COVID Respiratory Scale Category C1 (on high-flow nasal oxygen) or C2 [on non-invasive ventilation (NIV)] disease. An absolute contra-indication to administration of tocilizumab was acute severe infection from sources other than severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [5].

The aim of this study was to describe the characteristics and outcomes of patients with severe COVID-19 who received tocilizumab in critical care at the study institution. Furthermore, this study evaluated whether there were any differences in length of stay or mortality between those patients with severe COVID-19 who received tocilizumab and those who did not.

Methods

Study design, study site and population

This retrospective observational review was conducted at University Hospital Limerick (UHL), a 531-bed tertiary referral hospital in the Mid-West of Ireland which serves a population of approximately 473,000. UHL comprises part of the University of Limerick Hospitals Group (ULHG), which also includes three Level 2 hospitals (Ennis Hospital, Nenagh Hospital and St. John's Hospital, Limerick), one maternity hospital (University Maternity Hospital Limerick) and one orthopaedic hospital (Croom Orthopaedic Hospital). Critical care services for ULHG are centralized in UHL, with 12 beds in the ICU and 16 beds in the high-dependency unit. Hospital-acquired bacterial and fungal infections and their management at these facilities have been reported previously [6–8].

Patients included in this review were adults (age >18 years) admitted to critical care in UHL diagnosed with severe or critical COVID-19 who received tocilizumab between 1st January and 31st December 2021. Diagnosis was determined by detection of SARS-CoV-2 RNA by nasopharyngeal swabs using real-time polymerase chain reaction (RT-PCR). Guidance was provided on the staff app regarding the process for convening an urgent MDT when tocilizumab was being considered as a treatment modality. The Pharmacy Department only dispensed tocilizumab after confirmation of MDT approval.

Data collection and outcomes

The primary outcomes of interest were mortality and length of stay for patients with severe COVID-19 in critical care who received tocilizumab compared with those who did not receive tocilizumab. The secondary objective was to describe the characteristics and outcomes of patients with severe COVID-19 in critical care who received tocilizumab.

A retrospective chart review was performed for all patients who received tocilizumab. In addition, data were gathered from a number of additional sources. Radiology results were obtained from McKesson Radiology Manager at ULHG. Laboratory data (microbiology/serology/haematology and biochemistry results), in addition to notes from daily microbiology/critical care ward rounds, were extracted from the Laboratory Information Management System (iLab V6.1b06, Dedalus, Milan, Italy). Additional microbiology results, including SARS-CoV-2 PCR results from community test centres, were obtained from clinical surveillance software (ICNET, Baxter Healthcare, Deerfield, IL, USA). Data on respiratory requirements were obtained from ICU electronic records. Admission and discharge data, along with mortality data, were gathered from patient management software (iPM v5.0, CSC Technologies). Prescribing data were retrieved from pharmacy and chart review.

Selection criteria for tocilizumab

Only patients with severe COVID-19 infection who were in the ICU requiring organ support were included in this study. Before tocilizumab was administered, patients were assessed for evidence of severe sepsis, including measurement of serum procalcitonin (PCT); a PCT level >2 μg/L was a contra-indication to administration of tocilizumab. Microbiology culture results were also examined for evidence of infection, and it was recommended that patients underwent hepatitis B and human immunodeficiency virus (HIV) serological testing and interferon-gamma release assay (IGRA) testing. As this was not a randomized controlled trial, membership of the MDT varied over the duration of the study, and there may have been differences in the assessment of eligibility for tocilizumab treatment, especially when it was an entirely unfamiliar treatment modality.

Data collection from the tocilizumab group

Demographic data included age, gender and co-morbidities. Times from symptom onset and COVID-19 diagnosis to administration of tocilizumab, from hospital admission to critical care admission, and from hospital admission to tocilizumab administration, were calculated. Data on ventilation requirements pre- and post-tocilizumab administration and on concomitant treatments (including remdesivir, dexamethasone, antibiotics and antifungals) were also collected. Laboratory data collected pre- and post-tocilizumab administration

included leukocyte and lymphocyte levels, C-reactive protein (CRP), ferritin, d-dimer and IL-6 levels. Data on vaccination status were not collected as the national immunization programme for COVID-19 was still in its infancy.

Definitions of secondary infections

Hospital-acquired pneumonia (HAP) was defined as pneumonia that occurred ≥48 h after admission to hospital that was not incubating on admission [9]. Ventilator-associated pneumonia (VAP) was defined as HAP that occurred >48 h after endotracheal intubation [9]. In this study, no distinction was made between HAP and VAP. Pneumonia was defined as the presence of a new lung infiltrate on imaging, along with clinical evidence that would support an infectious aetiology such as new fever, purulent sputum, increasing respiratory requirements and a rising white cell count. This was correlated with microbiological findings which included sputum, tracheal aspirate and blood cultures.

Catheter-associated urinary tract infection was determined by laboratory detection of bacteriuria, in conjunction with clinical signs and symptoms suggestive of a urinary tract infection [10].

Invasive fungal infection was determined to be proven or probable based on the updated consensus definitions of invasive fungal disease from the European Organisation for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium — specifically, the definitions that arose from the intensive care working group [11,12]. In the case of invasive aspergillosis, in addition to specified host factors, this included mycological evidence of *Aspergillus* spp., galactomannan antigen index >0.5 in plasma/serum and/or galactomannan antigen index >0.8 in bronchoalveolar lavage fluid, in addition to clinical or radiological features consistent with an otherwise unexplained pulmonary infection.

Statistical analysis

Analyses were performed using Excel Version 15.22 (Microsoft Corp., Redmond, WA, USA).

Results

Characteristics of patients receiving tocilizumab

Seventy-four patients were admitted to the ICU at UHL with COVID-19 during the study period, accounting for 18.2% of UHL ICU admissions in 2021. Of these, 41 patients received tocilizumab. The majority were male (63%), with a median age of 64 years (range 21–77 years). Seventy-one percent of patients had at least one co-morbidity, and the most common co-morbidities were obesity (44%), cardiovascular disease (42%) and respiratory disease (32%). Most obese patients (83%) had at least one other co-morbidity. Diabetes mellitus was reported in 17% of patients, and only one patient (2%) had a history of pre-existing renal disease (on haemodialysis). Seven patients were considered immunocompromised with medical conditions that included chronic lymphocytic leukaemia (*N*=2), systemic lupus erythematosus (*N*=2), rheumatoid arthritis (*N*=2) and sarcoidosis (*N*=1). No patients had a history of liver disease (Table I).

Date of symptom onset prior to hospital admission was known for 18 (44%) patients; of these, median time from symptom onset to hospital admission was 7 (range 2–15) days. Date of SARS-CoV-2 PCR positivity was known for all patients, and the majority (71%) were diagnosed in the community prior to hospital admission. Median time from diagnosis to hospital admission was 4 (range 1–31) days. Median time from hospital admission to critical care admission was 1 day (range 1–10 days). Median time from hospital admission to tocilizumab administration was 2 (range 1–10) days.

Ninety-eight percent of patients who received tocilizumab also received dexamethasone, and 63% also received remdesivir. Empiric antibiotics and antifungals were prescribed in 100% and 34% of cases, respectively.

Respiratory requirements

Prior to tocilizumab administration, 27% of patients (*N*=11) required mechanical ventilation. Of the non-ventilated group, 20% required high-flow nasal oxygen/AIRVO and 80% were maintained on NIV. Post-tocilizumab administration, 18 further patients progressed to mechanical ventilation (71% total), and the remaining 12 patients (29%) did not. All patients had chest imaging consistent with COVID-19 pneumonitis.

Markers of systemic inflammation prior to tocilizumab administration

Almost all patients (98%) had an elevated CRP, with a median value of 96 (range 2–283) mg/L. A CRP value > 75 mg/L was observed in 61% of patients. Serum ferritin was elevated in 78% of cases, with a median of 843 (range 14–4745) ng/mL. D-dimer was elevated in the majority of cases (76%), with a median of 1.76 (range 0.4–>4) μg/mL; however, it was noted to be in the normal range in 24% of cases. Eighty-one percent of patients were noted to be lymphopenic, with a median of 0.53 (range 0.21–284) x 10^9/L. IL-6 was elevated in all but one patient prior to tocilizumab administration, with a median of 36 (range 3–3770) ng/L.

Evidence of severe infection other than SARS-CoV-2 infection prior to tocilizumab administration

No patient demonstrated microbiological evidence of either bacterial or fungal infection prior to administration of tocilizumab. Procalcitonin was measured in 90% of patients, and the median level was 0.26 (range <0.06–1.88) μg/L. Two patients had procalcitonin levels > 2 μg/L on ICU admission; both were treated with empiric antibiotics for 3–5 days prior to administration of tocilizumab, and neither exhibited any evidence of bloodstream, urinary tract or respiratory infection before receiving tocilizumab. Hepatitis B and HIV serological testing (all negative) was performed for 81% and 78% of patients, respectively. Only 32% underwent IGRA testing; of these, 46% were negative, 15% were indeterminate and 39% were unprocessed due to technical issues.

Characteristics of the non-tocilizumab group

Thirty-three patients with COVID-19 were admitted to the ICU and did not receive tocilizumab. The majority were male (58%), with a median age of 63 (range 32–81) years. The majority (85%)

Table I
Overview of intensive care unit (ICU) patients (1st January–31st December 2021)

		COVID-19 ICU patients		General ICU patients
		Tocilizumab	No tocilizumab	
	N	41	33	332
Age (years)	Median	64	64	64
	Range	21–77	32–81	16–88
Gender	% Male	63	55	60
Co-morbidities (%)	Respiratory	32	36	-
	Cardiovascular	42	42	-
	Diabetes mellitus	17	39	-
	Renal disease	2	15	-
	Liver disease	0	6	-
	Haem/oncology	5	12	-
	Immunosuppressed	17	18	-
	Obesity	44	21	-
Length of ICU stay (days)	*All patients*			
	Median	18	9	4
	Range	1–95	1–103	1–90
	Survivors			
	Median	21	9	5
	Range	3–95	2–103	1–74
Length of hospital stay (days)	*All patients*			
	Median	23	23	15
	Range	7–109	1–154	1–253
	Survivors			
	Median	45	34	20
	Range	9–109	6–154	1–253

COVID-19, coronavirus disease 2019.

had at least one co-morbidity, with cardiovascular disease (42%), diabetes mellitus (39%) and respiratory disease (36%) being the most common co-morbidities. Of this cohort, 21% were obese (Table I). Three patients had newly diagnosed malignancies, four were receiving immunosuppressive therapies for inflammatory arthritis, and one had a history of renal transplant. Two patients were pregnant and one had a history of hepatitis B. The majority (58%) of cases were diagnosed in the community, 30% in the emergency department, and there were four cases (12%) of hospital-acquired COVID-19. Excluding the hospital-acquired cases, median time from PCR positivity to hospital admission was 4 (range 1–28) days, and median time from PCR positivity to ICU admission was 6 (range 1–39) days. Thirty-nine percent of patients were admitted to the ICU within 24 h of hospital admission. Three (9%) patients did not have radiological findings consistent with COVID-19 (one case of hospital-acquired COVID-19 with small bowel perforation and only mild respiratory symptoms, one case of *Neisseria meningitidis* sepsis, and one case of diabetic ketoacidosis with mild respiratory symptoms). Most patients (88%) received dexamethasone, 52% received remdesivir, and all received empiric antibiotics. Details of laboratory markers and respiratory requirements of these patients are shown in Tables II and III, respectively.

Secondary infections

Twenty-six patients who received tocilizumab had a significant bacterial or fungal infection, compared with 13 patients who did not receive tocilizumab [odds ratio (OR) 2.67, 95% confidence interval (CI) 1.0373–6.8551; P=0.0417] (Table IV).

Overall, 38 patients (51%) with COVID-19 developed a bacterial infection post-ICU admission, compared with 36 patients (11%) from the general ICU population during the same period (OR 8.68, 95% CI 4.89–15.38; P<0.0001). Twenty-five (61%) patients who received tocilizumab developed a bacterial infection, with 16 (39%) having more than one bacterial infection. There were 24 cases of pneumonia, 19 bloodstream infections and five catheter-associated urinary tract infections. Median time from hospital admission to bacterial infection was 14 (range 3–102) days, and median time from administration of tocilizumab to bacterial infection was also 14 (range 1–95) days. Patients were predominantly male (72%), and median age was 65 (range 39–77) years. Eighty-one percent of patients had more than one co-morbidity, and 46% of these patients died.

Of the 33 patients who did not receive tocilizumab, 13 (39%) developed a bacterial infection during their ICU stay, with seven (21%) having more than one infection. There were 10 cases of pneumonia, nine bloodstream infections, four catheter-associated urinary tract infections and one *Clostridioides difficile* infection. Median time from hospital admission to bacterial infection was 22 days. There was a slight female predominance (54%), and median age was 63 (range 29–77) years. All patients had at least one co-morbidity, and 46% of these patients died.

Table II
Laboratory markers in intensive care unit (ICU) patients with coronavirus disease 2019 (COVID-19) (January–December 2021)

	COVID-19-positive ICU patients	
	Tocilizumab	No tocilizumab
N	41	33
CRP (mg/L)		
Median	96	130
Range	2–283	6–319
Ferritin (ng/mL)		
Median	843	830
Range	14–4745[a]	54–2856[b]
D-dimer (μg/mL)		
Median	1.76	2.45
Range	0.4–4.0	0.36–4.0[c]
IL-6 (ng/L)		
Median	36	67
Range	3–3770	8–50,000
White cell count (x 10^9/L)		
Median	9.66	9.25
Range	2.57–327	2.77–33.04
Lymphocytes (x 10^9/L)		
Median	0.53	0.68
Range	0.21–284	0.32–5.9
Procalcitonin (μg/L)		
Median	0.26	0.25
Range	0.06–1.88[d]	0.06–100[e]

CRP, C-reactive protein; IL-6, interleukin-6.
[a] Data from 35/41 patients.
[b] Data from 31/33 patients.
[c] Data from 32/33 patients.
[d] Data from 37/41 patients.
[e] Data from 30/33 patients.

Fungal infections

Fungal infections were more common in the tocilizumab cohort (seven cases) than in the non-tocilizumab cohort (one case) (OR 6.59, 95% CI 0.77–56.6; *P*=0.0857). Seventy-five percent of those with probable invasive fungal disease survived (*N*=3), while 67% of those with candidemia survived (*N*=2).

Length of stay and mortality

Amongst survivors, median length of stay in critical care was 21 (range 3–95) days for the tocilizumab group, compared with 9 (range 2–103) days for the non-tocilizumab group. Median length of hospital stay for survivors was 45 (range 9–109) days for the tocilizumab group compared with 34 (range 6–154) days for the non-tocilizumab group.

Thirty-day mortality was 29% for the tocilizumab group and 36% for the non-tocilizumab group (*P*=0.5196). Sixty-day mortality was 37% for the tocilizumab group and 42% for the non-tocilizumab group (*P*=0.6138).

Discussion

Tocilizumab is one of a limited number of treatment options available for COVID-19. It is a humanized monoclonal anti-IL-6 antibody that is licensed for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis and giant cell arteritis [13,14]. It acts by preventing IL-6 from binding to soluble and cell-associated IL-6 receptors, thereby inhibiting IL-6-mediated signalling. Studies have shown that IL-6 levels are elevated in patients with COVID-19 [15], and it is postulated that tocilizumab may be an effective therapy in COVID-19 due to its ability to dampen down the cytokine storm that accompanies severe COVID-19 [15].

Studies of tocilizumab in COVID-19 have given conflicting results, which may reflect lack of standard protocols for its use [16–20]. Initial trials demonstrated no clear benefit of tocilizumab monotherapy on survival, length of hospital stay, need for mechanical ventilation, disease progression or time to recovery [21–26]. The REMAP-CAP study was an open-label international randomized trial of 803 adult patients with severe COVID-19 in ICUs requiring either respiratory or cardiovascular support; patients were randomized to receive one of two IL-6 inhibitors — tocilizumab or sarilumab — compared with standard care within 24 h of ICU admission. More than 80% of patients also received glucocorticoids, and approximately one-third of patients (33%) received remdesivir. Both IL-6 inhibitors in this study were found to reduce 28-day in-hospital mortality compared with standard care, and tocilizumab was found to reduce both length of ICU stay and mortality, with the effect being greater in patients who also received steroids [27]. Subsequently, the RECOVERY trial showed that tocilizumab, administered together with corticosteroids,

Table III
Supplementary treatments in coronavirus disease 2019 (COVID-19) infection

		COVID-19-positive ICU patients	
		Tocilizumab	No tocilizumab
	N	41	33
Remdesivir (%)		63	52
Dexamethasone (%)		98	88
Imaging consistent with COVID-19 infection (%)		100	91
Respiratory requirements on admission to ICU (%)	High flow/AIRVO	15	36
	NIV	59	52
	Intubation	27	12
	Progression to intubation	71	67

ICU, intensive care unit; NIV, non-invasive ventilation.

Table IV
Bacterial and fungal infections amongst intensive care unit (ICU) patients at University Hospital Limerick (January–December 2021)

		COVID-19 ICU patients		General ICU patients
		Tocilizumab	No tocilizumab	
	N	41	33	332
Bacterial infection, % (*N*)	HAP	59 (24)	30 (10)	8 (27)
	BSI	46 (19)	27 (9)	5 (17)
	CAUTI	12 (5)	12 (4)	3 (9)
	Clostridioides difficile	0 (0)	3 (1)	1 (3)
	SSTI	2 (1)	0 (0)	0 (0)
Fungal infection, % (*N*)	IFD	10 (4)	3 (1)	1 (2)
	Candidemia	7 (3)	0 (0)	1 (3)
Time to detection of first bacterial infection (days)	From hospital admission			
	Median	14	22	-
	Range	3–102	3–94	-
	From tozilizumab administration			
	Median	13	-	-
	Range	1–95	-	-

COVID-19, coronavirus disease 2019; HAP, hospital-acquired pneumonia; BSI, bloodstream infection; CAUTI, catheter-associated urinary tract infection; SSTI, skin and soft tissue infection; IFD, invasive fungal disease.

reduced the relative risk of death from COVID-19 at day 28 by 14%, and the absolute risk of mortality by 4% in an intention-to-treat analysis [28]. No mortality benefit was seen when tocilizumab was administered as monotherapy. A limitation of the RECOVERY trial is that 17% of patients randomized to receive tocilizumab did not receive it; an observation that the authors could not explain. The present study was not powered to assess outcomes, but contrary to the REMAP-CAP and RECOVERY trials, this study found an increased length of hospital stay in patients receiving tocilizumab. This may be because the groups were not balanced; for example, 27% of the tocilizumab group were intubated on ICU admission compared with 12% of the non-tocilizumab group.

Tocilizumab has been licenced for the use in the European Union since 2009 for adults with moderate-to-severe rheumatoid arthritis and children with juvenile idiopathic arthritis. It is also used in patients with giant cell arteritis. Adverse events in this population have been well characterized. Serious and occasionally fatal infections can occur, and can include tuberculosis and viral reactivation [29–33]. Morel *et al*. [29] reported 4.7 serious infections (infections requiring hospitalization or intravenous antibiotics, or resulting in death) per 100 patient-years in patients with rheumatoid arthritis, with a mean time of 12.8 months from administration of tocilizumab to diagnosis of the first serious infection. Respiratory and skin/soft tissue infections were most common. There were three deaths due to septic shock secondary to pyelonephritis, *Pneumocystis jiroveci* pneumonia and *Haemophilus influenzae* pneumonia. All three patients had serious co-morbidities, were aged >65 years and were receiving concomitant methotrexate treatment. Genovese *et al*. [31] reported a similar rate of serious infections in five randomized controlled trials of patients with moderate-to-severe rheumatoid arthritis receiving tocilizumab of 4.5 per 100 patient-years. Again, respiratory and skin/soft tissue infections were most common. The nine serious infections mainly comprised invasive fungal infections; three patients with invasive candidiasis died. A further nine patients (0.1 per 100 patient-years) developed tuberculosis, only one of which was previously known to have latent tuberculosis. A higher rate of serious infection (5.74 per 100 patient years) was reported by Jones *et al*. [30].

A systematic review of tocilizumab in patients with COVID-19 reported no increased risk of infections in patients receiving tocilizumab [34]. Similarly, a meta-analysis of 10,930 hospitalized patients with COVID-19 from 27 randomized controlled trials found no association between IL-6 antagonists (including tocilizumab) and risk of 28-day infection [35]. This is in contrast to other reviews which have demonstrated mixed results with varying levels of significance with respect to risk of infection and use of tocilizumab [36]. This is in contrast to the authors' experience of a significant increase in infections in patients receiving tocilizumab, two of whom died from their secondary infections.

This study has several limitations as it was a small, single-centre retrospective observational study. It would seem that the tocilizumab group may have had more severe illness, which may account for the prolonged ICU stay. In turn, this may have increased the risk of ICU-acquired (particularly medical-device-related) infections that were not related to the effects of tocilizumab.

In conclusion, this study shows that, although large series have not shown increased risk of serious infections in COVID-19 cases receiving tocilizumab, it is important that individual centres are vigilant in monitoring patients for serious bacterial and fungal infections, because the cohort of patients treated may be at increased risk of infection for reasons other than a direct immunosuppressive effect of tocilizumab.

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