Record of the Tocilizumab ad hoc Advisory Group

Meeting held via videoconference on 21 April 2021

Present from the ad hoc tocilizumab Advisory Group

Mark Weatherall (Chair)
Bruce King (PTAC Member)
Graham Mills
Marius Rademaker (PTAC Member)
Stephen Munn (PTAC Member)

Observer
Eamon Duffy

Apologies:
Brian Anderson
Gillian Bishop
Sean Hanna

1. Welcome and introduction

1.1. It was noted that the purpose of this *ad hoc* Advisory Group was to provide PHARMAC with clinical advice on an application received for use of tocilizumab in moderate-severe COVID-19.

1.2. It was noted that the process for funding of any costs related to COVID-19 treatments would be managed separately to the Combined Pharmaceutical Budget (CPB) and that PHARMAC intends to develop a process to enable the timely assessment of pharmaceutical treatments for COVID-19, tailored to the relevant funding and clinical context.

1.3. This record is a summary of relevant discussion of the key issues by the *ad hoc* Tocilizumab Advisory Group meeting and is not to be considered an exhaustive detailed account of all discussions.

2. Tocilizumab use in moderate-severe COVID-19

Application

2.1. The Advisory Group reviewed the clinician application for tocilizumab for the treatment of patients who have been hospitalised with moderate to severe COVID-19.

2.2. The Advisory Group took into account, where applicable, PHARMAC's relevant decision-making framework when considering this item.

Recommendation

2.3. The Advisory Group **recommended** that tocilizumab for the treatment of moderate to severe COVID-19 be made available, subject to the following Special Authority / Hospital Restriction criteria:

Restricted
Indication – moderate-severe COVID-19
All of the following:
1. Patient has confirmed (or strongly clinically suspected) severe COVID-19; and
2. Oxygen saturation of <92% on room air, or requiring supplemental oxygen; and
3. Patient has significant laboratory markers of systemic inflammation (eg CRP, PCT or ferritin); and
4. Patient is receiving adjunct systemic corticosteroids, or systemic corticosteroids are contraindicated; and
5. Tocilizumab is to be administered at doses no greater than 8mg/kg IV for a maximum of one dose.

2.5 In making this recommendation, the Advisory Group considered the high health need and limited treatment options for patients with moderate to severe COVID-19, the equity implications of COVID-19 and likelihood of a higher mortality rate for patients with comorbidities, the safety and efficacy profile of tocilizumab when used concomitantly with systemic corticosteroids for COVID-19 and likely measurable health benefits.

2.5.1 Members noted tocilizumab use as a treatment for moderate to severe COVID-19 is an unapproved indication, and **recommended** PHARMAC staff engage with Medsafe regarding treatment with tocilizumab in this setting.

2.5.2 PHARMAC staff advised that no priority ranking (within the context of treatments for COVID-19) was sought by PHARMAC, reflecting the rapidly evolving evidence for treatments in COVID-19 and separate funding outside the CPB, and thus the *ad hoc* group did not discuss a priority ranking.

2.6 The Advisory Group reiterated this was an area of rapidly advancing evidence and knowledge and specified that its recommendation should be considered valid for a maximum of 12 months, noting this was based on currently available data from published studies and could be subject to change should new data become available, warranting further review.

Discussion

2.7 The Advisory Group noted that the inflammatory response and related lung injury associated with SARS-CoV2 (COVID-19) has been the subject of interest and research since early 2020, leading to the investigation of the inflammatory markers thought to be up-regulated in patients with moderate to severe COVID-19 as clinical predictors of mortality. The Advisory Group noted the May 2020 study by Ruan et al. which reported elevated levels of interleukin-6 (IL-6) in patients who died from COVID-19 (Ruan et al. Intensive Care Med. 2020;46:846-8). The Advisory Group noted that severe COVID-19 infection was associated with cytokine release syndrome in some patients, which increases IL-6 signalling and noted that agents that block the signal transduction pathway of IL-6, such as tocilizumab, have been identified as possible treatments for patients with moderate to severe COVID-19 (Moore & June. Science. 2020;368:473-4).

2.8 The Group noted seven studies relating to the use of tocilizumab in patients with COVID-19, noting early results in the absence of systemic corticosteroid use indicated poor effectiveness; however, later studies indicated increasing levels of benefit, associated with increasing prevalent levels of concurrent systemic corticosteroid use:

2.8.1 Salvarani et al. JAMA Intern Med. 2021;181:24-31: a randomised clinical trial of hospitalised adult patients with COVID-19 pneumonia, partial pressure of arterial oxygen to fraction of inspired oxygen (Pao2/Fio2) ratio between 200 and 300 mm Hg, and an inflammatory phenotype defined by fever and elevated

C-reactive protein receiving tocilizumab as a single agent or standard care (N=126, 4% of patients received treatment with corticosteroids). The study reported no benefit in disease progression.

2.8.2 Stone et al. N Engl J Med. 2020;383:2333-44: a randomised, double-blind, placebo-controlled trial of 243 patients with confirmed severe SARS-CoV-2 infection, hyperinflammatory states, and at least two of the following signs: fever (body temperature >38°C), pulmonary infiltrates, or the need for supplemental oxygen in order to maintain an oxygen saturation greater than 92%, assigned to receive a single dose of tocilizumab or placebo (N=243, 10% of patients received corticosteroids). The study reported that tocilizumab was not effective for preventing intubation or death in moderately ill hospitalised patients with COVID-19.

2.8.3 Rosas et al. N Engl J Med. 2021;NEJMoa2028700: a randomised, placebo-controlled trial of patients hospitalised with severe COVID-19 pneumonia received a single dose of tocilizumab or placebo (N=438, 42% of patients had received steroids). The study reported that the use of tocilizumab did not result in significantly better clinical status or lower mortality compared to placebo at 28 days.

2.8.4 Hermine et al. JAMA Intern Med. 2021;181:32-40: a randomised controlled trial involving patients with COVID-19 and moderate or severe pneumonia requiring at least 3 L/min of oxygen but without ventilation or admission to the intensive care unit treated with tocilizumab or standard care alone (N=131, 48% of patients had received corticosteroids). The study reported that tocilizumab did not reduce World Health Organization 10-point Clinical Progression Scale (WHO-CPS) scores lower than 5 at day 4, but might have reduced the risk of non-invasive ventilation, mechanical ventilation, or death by day 14. The crucial end point showed no difference on day 28 mortality.

2.8.5 Salama et al. N Engl J Med. 2021;384:20-30: a randomised controlled trial of patients hospitalised with COVID-19 pneumonia who were not receiving mechanical ventilation treated with standard care plus one or two doses of either tocilizumab or placebo (N=389, 83% of patients received corticosteroids). The study reported that treatment with tocilizumab reduced the likelihood of progression to mechanical ventilation or death, but it did not improve survival.

2.8.6 Gordon et al. N Engl J Med. 2021;NEJMoa2100433: a randomised placebo-controlled trial (REMAP-CAP trial) of patients with COVID-19, within 24 hours after starting organ support in the intensive care unit (ICU), receiving tocilizumab, sarilumab or standard care (N=353, 88% of patients received corticosteroids). The study reported that treatment with tocilizumab led to a significant increase in 90-day survival compared to standard care (HR for death 1.59; 95% CI 1.24 to 2.05).

2.8.7 Horby et al. MedRxiv. 2021;21249258: a randomised, controlled, open-label, platform trial (RECOVERY trial) of patients including those receiving invasive mechanical ventilation, non-invasive respiratory support, and no respiratory support other than oxygen who received either tocilizumab or standard care (N=4116, 82 % of patients received systemic corticosteroids at randomisation). The study reported a significant improvement in the likelihood of discharge alive from hospital at 28 days regardless of other respiratory support (risk ratio 1.22; 95% CI 1.12 to 1.34; P<0.0001). The Group noted that there were only 3

serious adverse events attributed to the treatment drug in over 2,000 patients receiving tocilizumab.

2.9 The Advisory Group noted a March 18, 2021 updated Cochrane living systematic review of tocilizumab compared to standard care or placebo for mild, moderate, or severe COVID-19 (Ghosn et al. CDSR 2021;3:CD013881), which reported a relative risk of 0.89 (95% CI 0.82 to 0.97) for all-cause mortality at day 28. The Advisory Group also noted a meta-analysis of IL-6 concentrations in patients with COVID-19, reporting levels of IL-6 in COVID-19 patients less elevated than in other critical illnesses associated with elevated IL-6 (Leisman et al. Lancet Respir Med. 2020;8:1233-44). The Advisory Group considered that the comparatively lower relative risk reduction result reflects a modest effect of tocilizumab due to the comparatively low circulating IL-6 levels, despite the mechanistic explanation for tocilizumab effect.

2.10 The Advisory Group noted that systemic corticosteroids can inhibit the IL-6 pathway in COVID-19 patients, and that the degree of inhibition has prognostic importance. The Advisory Group considered systemic corticosteroids an important driver of reduction in symptom burden, hospital stay, and mortality, when administered with tocilizumab. The Advisory Group considered that in addition to the survival benefit associated with tocilizumab and systemic corticosteroid treatment, there would be a likely reduction in need for invasive ventilation, shorter length hospital stays, and a potential reduction in the need for COVID-19 related renal replacement therapy.

2.11 The Advisory Group considered that the strength and quality of evidence for the health benefits that may be gained from tocilizumab are of moderate to high quality and demonstrating a moderate clinical benefit. The Group considered that the strength of the evidence would be higher if earlier trials, where only a small proportion of patients received systemic corticosteroids, were excluded.

2.12 The Advisory Group considered that that there is no evidence to suggest that the benefit of tocilizumab is confined to any particular patient subgroup. It also considered the eligibility criteria used in the RECOVERY trial (oxygen saturation <92% and C-reactive protein ≥ 75mg/L) were appropriate to determine suitability for tocilizumab use. The Group noted only 19% of patients enrolled in the large RECOVERY cohort met the eligibility criteria for tocilizumab use and extrapolating from this data estimated that approximately 4% of all symptomatic COVID-19 patients might be eligible for tocilizumab in a New Zealand setting. The Group noted that, based on UK data, it was estimated that treatment would be suitable in approximately 50% of hospitalised patients; however, members considered hospital data may underestimate true incidence rates, noting some population groups such as the elderly are at risk of mortality from COVID-19 outside of hospital, e.g. in aged-care facilities.

2.13 The Advisory Group considered that, based on available data, approximately 4% of symptomatic COVID-19 cases may be eligible for tocilizumab, and that this may fluctuate depending on the prevalence of COVID-19 and population demographics. The Advisory Group also considered that in the case of a community outbreak in New Zealand, it is likely that public health measures would be quickly put in place, which would reduce the overall incidence of COVID-19 related hospitalisations.

2.14 The Advisory Group considered the health need of patients with moderate-severe COVID-19 to be high and noted that the 28-day mortality rate of patients in the RECOVERY trial who did not receive tocilizumab was 33% and the in-hospital

mortality rate of those in the REMAP-CAP trial who did not receive tocilizumab was 36%.

2.15 The Advisory Group noted a 2020 report summary investigating the characteristics of the COVID-19 outbreak in China, which reported that 81% of hospitalised cases were considered mild i.e. non-pneumonia and mild pneumonia; 14% severe i.e., dyspnoea, respiratory frequency ≥30/min, blood oxygen saturation ≤93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300 and/or lung infiltrates >50% within 24 to 48 hours; and 5% critical i.e., respiratory failure, septic shock, and/or multiple organ dysfunction or failure (Wu & McGoogan. JAMA. 2020;323:1239-42). This is consistent with around 20% of hospitalised COVID-19 patients having moderate to severe disease.

2.16 The Advisory Group noted that 18% of family members of a symptomatic COVID-19 case contract COVID-19 themselves in the absence of vaccination (Madewell et al. JAMA Netw Open. 2020;3:e2031756), indicating there is a substantial risk that such families will suffer further COVID-19 infection with the associated discomfort of self or mandated isolation with or without additional economic hardship, noting the impact of this is yet to be quantified and reported in quality of life studies. The Advisory Group considered that use of tocilizumab would not affect subsequent emergence of transmitted cases within families but may provide direct and indirect benefits by reducing case fatality and morbidity rates.

2.17 The Advisory Group noted that New Zealand data does not indicate overrepresentation of COVID-19 incidence or mortality in any specific population group; however members noted a 2020 study combining existing demographic and health data for ethnic groups in New Zealand to estimate inequities in COVID-19 infection fatality rates (IFR) in New Zealand by ethnicity (Steyn et al. N Z Med J. 2020;133:28-39). The Advisory group noted that this study estimated infection mortality rate for Māori could be 50% higher than that of non-Māori, and considered this could be even higher depending on the relative contributions of age, residence (including household composition and crowding) and underlying health conditions to mortality risk from COVID-19. The Advisory Group further considered that Pacific populations share similar co-morbidity profiles etc. to Māori and would therefore also potentially have similarly higher fatality rates than NZ European cohorts. The Advisory Group noted that there is also a socioeconomic gradient associated with the prevalence of multimorbidity in New Zealand (Stanley et al. BMJ Open. 2018;8:e021689), and similar assumptions might apply to lower socio-economic groups.

2.18 The Advisory Group considered that funding tocilizumab for treatment of moderate-severe COVID-19 would have little impact on the health system, as a single dose would be given in hospital intravenously; however, it considered any reduction in length of hospital or ICU stay or ventilation would represent cost-savings for hospitals. Members noted that the extent of overall benefit from treatment may be less in some patient populations such as the very frail elderly, cognitive or neurologically impaired and palliative settings, and that treatment by way of escalation of care in these patient groups should be carefully considered by physicians.

2.19 The Advisory Group considered evidence supported a single dose (up to 8 mg per kg, maximum of 800 mg) of tocilizumab administered in conjunction with systemic corticosteroid treatment and considered there to currently be insufficient data to show benefit of a second dose or use without concomitant corticosteroids.

2.20 The Advisory Group noted concerns regarding the immunosuppressive effective of tocilizumab when used in severe infection but considered that the available trials reported a low risk of serious adverse events attributed to tocilizumab, e.g. only three adverse events in the RECOVERY trial. The Advisory Group however considered further investigation into these concerns may be required, noting that tocilizumab does not currently have New Zealand regulatory approval for use in this setting.

2.21 The Advisory Group noted that there are a number of treatments that have been, or are being, tested for safety and efficacy in patients with COVID-19. Of note, there are two recent randomised controlled trials of casirivimab plus imdevimab (monoclonal antibodies against the spike protein on COVID-19) which look promising in patients exposed to the virus. The Advisory Group considered that the landscape of treatments for COVID-19 is rapidly evolving, and that there is still a degree of uncertainty around the benefit of tocilizumab for the treatment of COVID-19.

Addendum: Following the meeting but prior to final publication of the record, the Advisory Group agreed to an amendment to the Special Authority / Hospital Restriction criteria relating to the demonstration of systemic inflammation in patients with moderate-severe COVID-19 who may obtain benefit from tocilizumab. This was informed by members' consideration of Huang et al. Ther Adv Respir Dis. 2020;14:14-14., and was agreed in order to enable timely and appropriate access to tocilizumab treatment.

Chair _____ Date _____