Tocilizumab in Hospitalized Patients with COVID-19

Journal Club

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Outline

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02 **RECOVERY trial**

03 **Apprasial**
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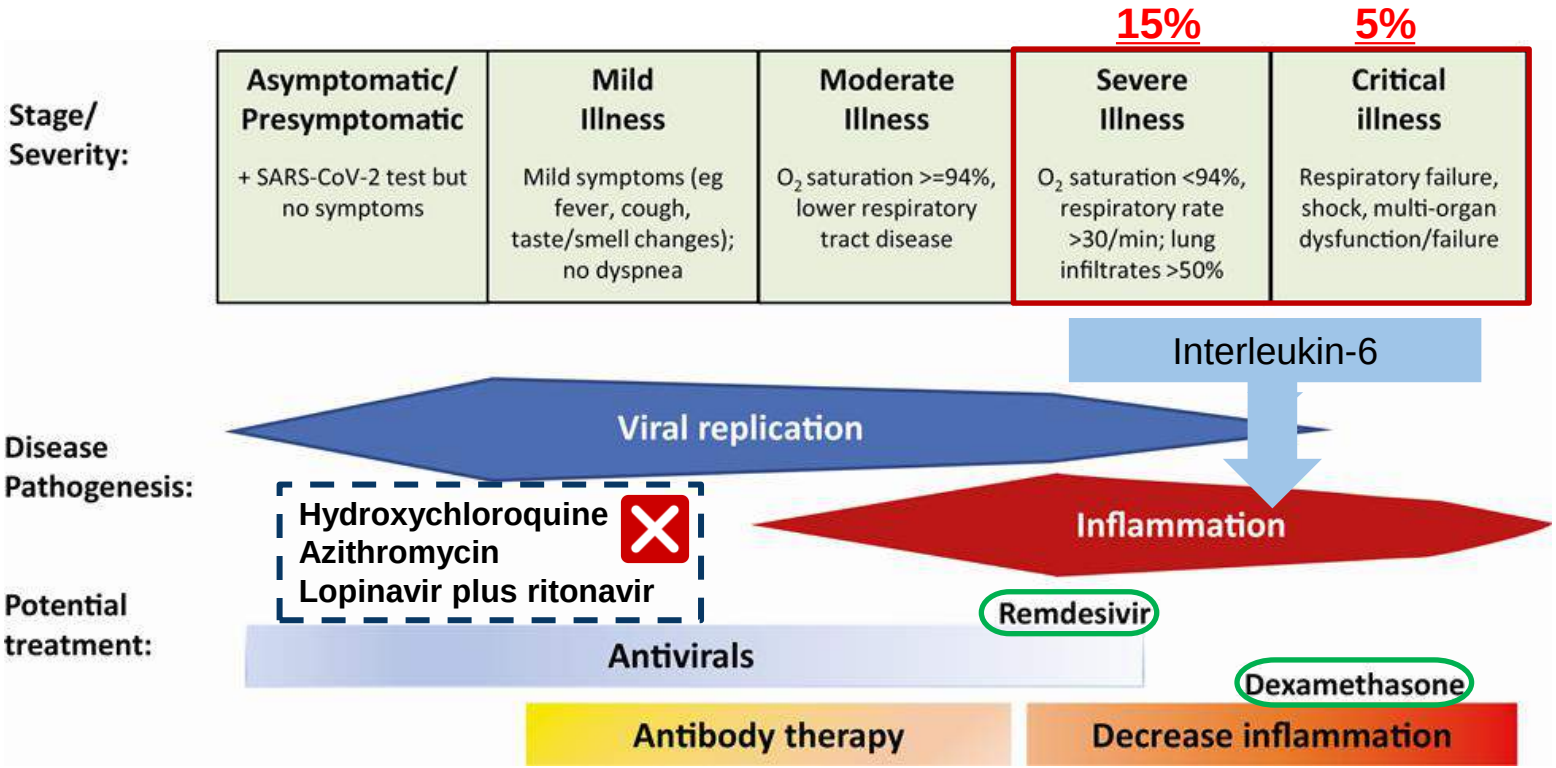
04 **Discussion**

01

Introduction

Role of Interleukin-6 Receptor Antagonists

The treatment of patients with Covid-19

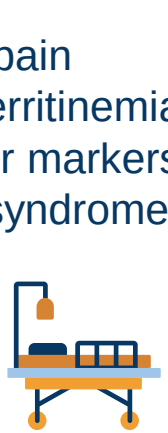


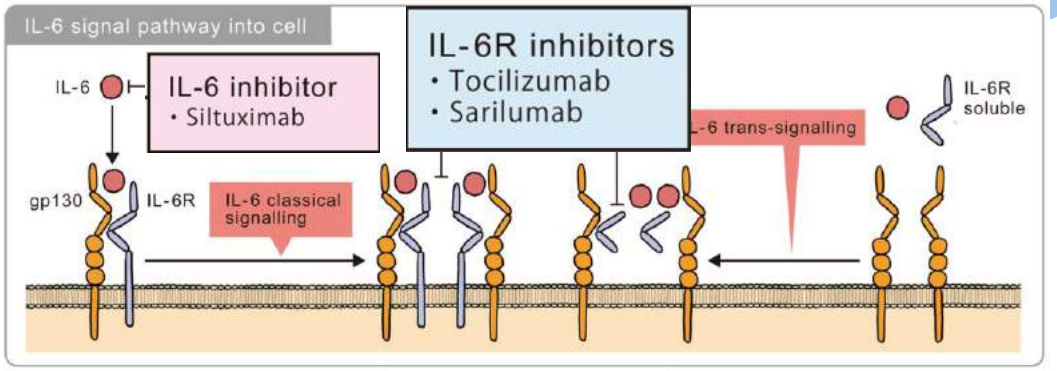
https://doi.org/10.1093/cid/ciaa1132
IDSA guideline updates on 2/11/2021

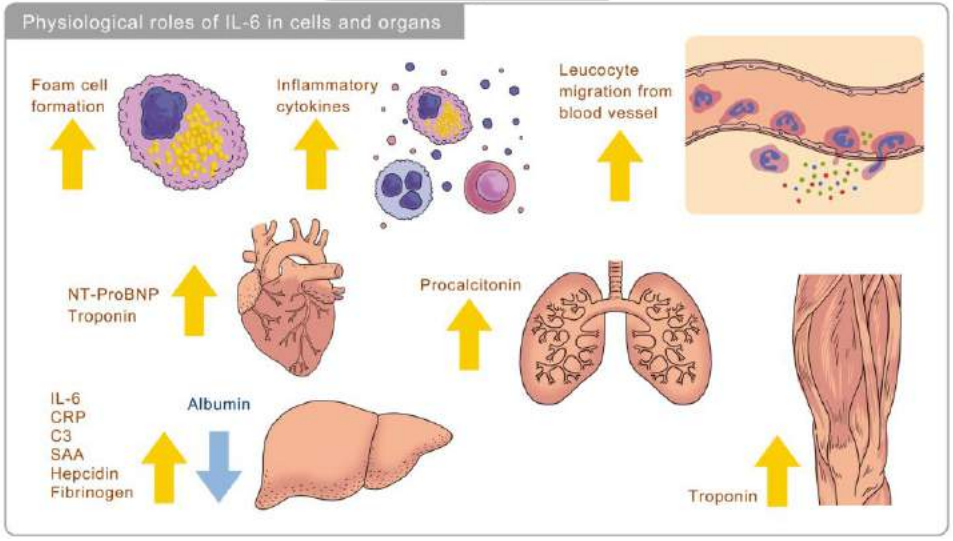
IL-6 signaling blockade for COVID-19

- Since IL-6 is released by immune cells including **macrophage and T cells**, they are activated by virus or bacteria or other immune cells.

- **Physiological role:**
- Fever, fatigue and muscle pain
- Thrombocytopenia, hyperferritinemia, and elevation of CRP (other markers)
- Acute respiratory distress syndrome
- Acute coronary syndromes
- Vasculitis
- Kidney, and liver injury
- Organ failure

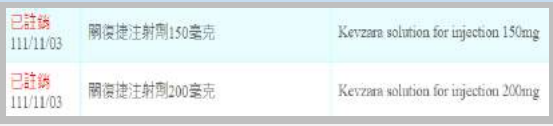






Hashizume Inflammation and Regeneration (2020) 40:24

Pharmacologic Inhibitors of IL-6 or IL-6R

Brand Name (Generic Name,Route)	TFDA-approved Indication	Cost
Actemra, IVD (**tocilizumab**) 	1. 類風濕性關節炎 2. 多關節性幼年型原發性關節炎 3. 全身性幼年型原發性關節炎	400 mg/vial: NTD 18,967 200 mg/vial: NTD 9,131 80 mg/vial: NTD 3,933
Actemra 162mg, SC (**tocilizumab**) 	1. 類風濕性關節炎 2. 巨細胞動脈炎	NTD 8,527/syr
Kevzara (**sarilumab**)	中至重度活動性類風濕性關節炎	
Enspryng 120mg, SC (**satralizumab**)	水通道蛋白4自體抗體陽性[anti-aquaporin-4 antibody positive]的泛視神經脊髓炎	無健保價
Sylvant, IVD (**siltuximab**)	多發性Castleman氏病(HHV-8陰性、HIV陰性)	無健保價 (100 mg/vial, 400 mg/vial)

02

RECOVERY trial

RECOVERY

Randomised Evaluation of COVID-19 Therapy

medRxiv
THE PREPRINT SERVER FOR HEALTH SCIENCES

The world's biggest randomized clinical trial of COVID-19 treatments

Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomized, controlled, open-label, platform trial

Posted on 2021/02/11
Authors: UK National Institute for Health Research Clinical Research Network and Oxford
Funding: Roche Products Ltd

Study design and participants

Aim

Evaluated the safety and efficacy of tocilizumab in adult patients admitted to hospital with COVID-19 with evidence of both hypoxia and systemic inflammation.

Study design

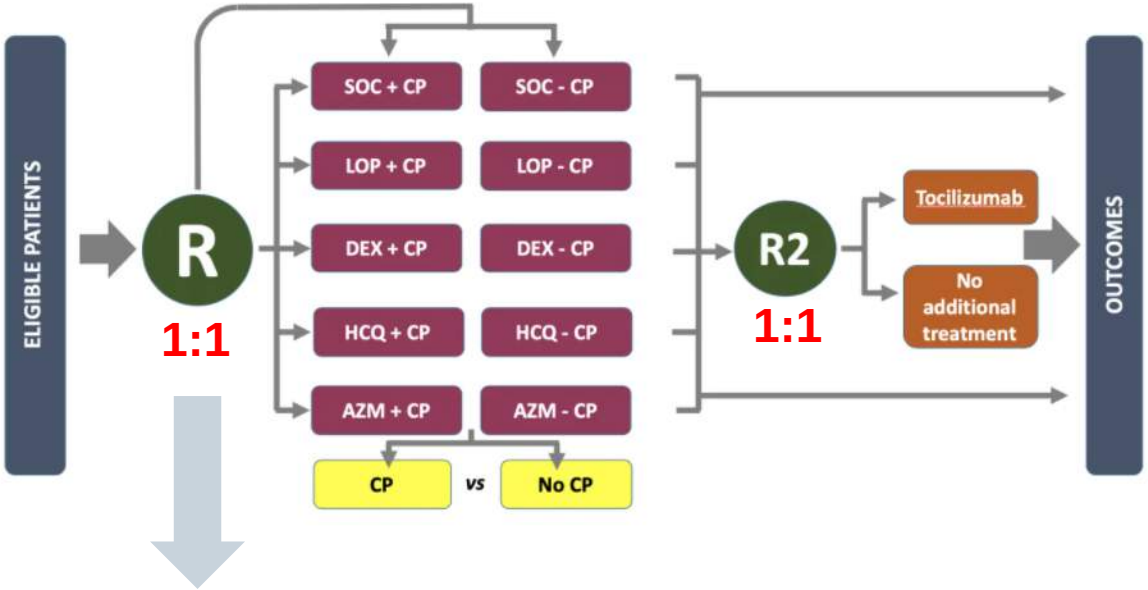
Individually randomised, controlled, open-label, platform trial

Participants

Eligibility

1) Hospitalised
2) SARS-CoV-2 infection associated disease (clinically suspected or laboratory confirmed)
3) No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial

Randomisation and masking



Eligibility in Randomisation 2

1) Recruited no more than 21 days.
2) Clinical evidence of progressive:
- oxygen saturation <92% on room air or requiring oxygen or significant systemic inflammation
- C-reactive protein ≥7.5 mg/dL

Central webbased randomisation service

- Part A: DEX- dexamethasone, HCQ-hydroxychloroquine, AZM-azithromycin, LOP-lopinovir/ritonivir, SOC-standard of care
- Part B : SOC or Convalescent plasma
- Part C: SOC or aspirin

Procedures

Procedures

- Tocilizumab should be given as a **single intravenous infusion** over 60 minutes in 100ml sodium chloride 0.9%.
- Dose determined by actual body weight**: 8 mg/kg (Max:800mg)**

Weight*	Dose
>40 and ≤65 kg	400 mg
>65 and ≤90 kg	600 mg
>90 kg	800 mg

- **A second dose** may be given ≥12 and <24 hours later if, in the opinion of the attending clinician, the patient's condition has not improved.

Duration of follow-up

- Followed up until death, discharge from hospital or **28 days after randomisation** (whichever is sooner).

Outcomes assessment

Primary objective: all-cause mortality at 28 days (ITT)

Secondary objectives:

- **Mortality:**
  - Time to discharge alive from hospital
- **Invasive mechanical ventilation:**
  - Receipt of invasive mechanical ventilation or death
  - Patients need for invasive mechanical ventilation or ECMO
  - Time to successful cessation of invasive mechanical ventilation
- **Organ failure related:**
  - Renal replacement therapy
- **Safety outcomes:**
  - cause-specific mortality
  - major cardiac arrhythmia

Patients not on invasive mechanical ventilation at baseline

Recovery trial:
- bleeding, new major cardiac arrhythmias
- Sudden worsening in respiratory status, hypotension
- Severe allergic reaction, significant fever

Statistical Analysis

Intention-to-treat analyses

Sample size calculated

- Recruitment of around 4000 patients to this comparison would provide 90% power
- Two-sided P=0.01 to detect a proportional reduction in 28-day mortality of one-fifth.

Risk ratios

- Estimates of rate and risk ratios are shown with 95% confidence intervals. All p-values are 2-sided and are shown without adjustment for multiple testing.

log-rank test

- For time-to-event analyses, each treatment group will be compared with the no additional treatment group using the log-rank test. Kaplan-Meier estimates for the time to event will also be plotted.

RESULTS_ Flow of participants

Study period: Between 14 April 2020 and 24 January 2021

RECOVERY trial: 4116 (19%) of 21550 patients enrolled into at one of the 131 sites in the UK participating

Group:

- 2022 patients were randomly allocated to tocilizumab
- 2094 were randomly allocated to usual care

Loss follow up

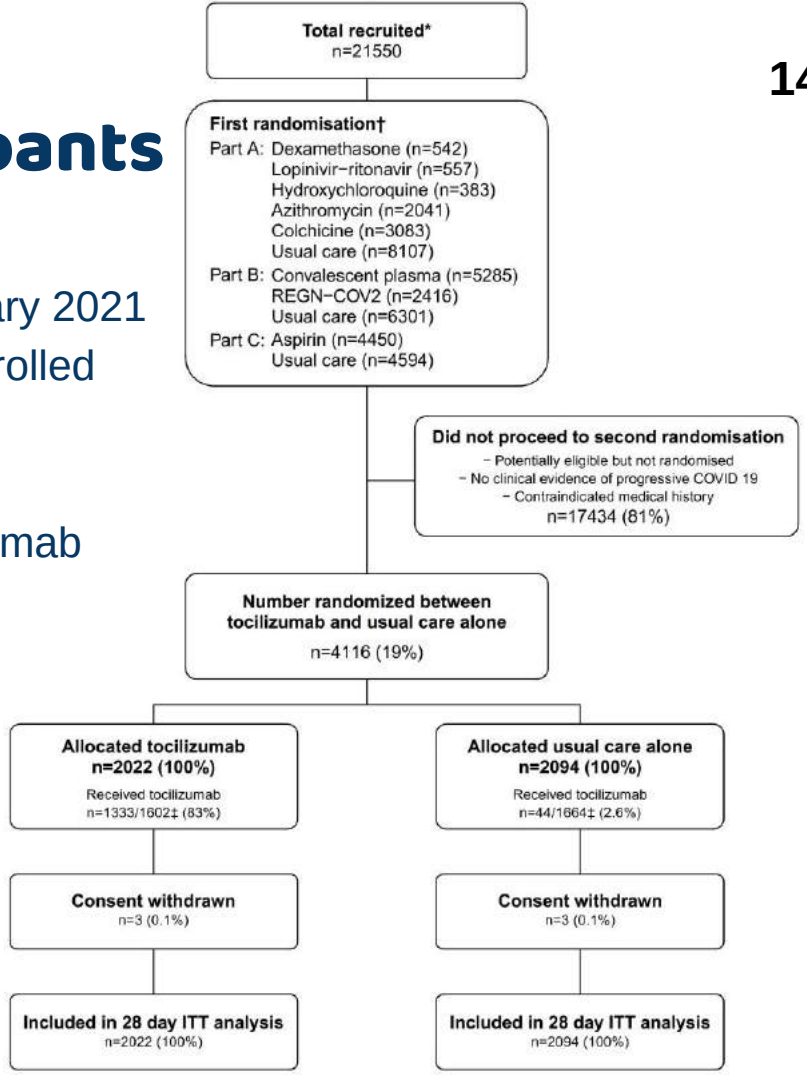
Tocilizumab: 0.1%

Usual care alone: 0.1%

Compliance data available

Tocilizumab: 1602 (79%)

Usual care alone: 1664 (79%)



RESULTS_ Flow of participants

Study period: Between 14 April 20

RECOVERY trial: 4116 (19%) of 21

into at one of the 131 sites in the UI

Group:

- 2022 patients were randomly all
- 2094 were randomly allocated to

Loss follow up

Tocilizumab: 0.1%

Usual care alone: 0.1%

Compliance data available

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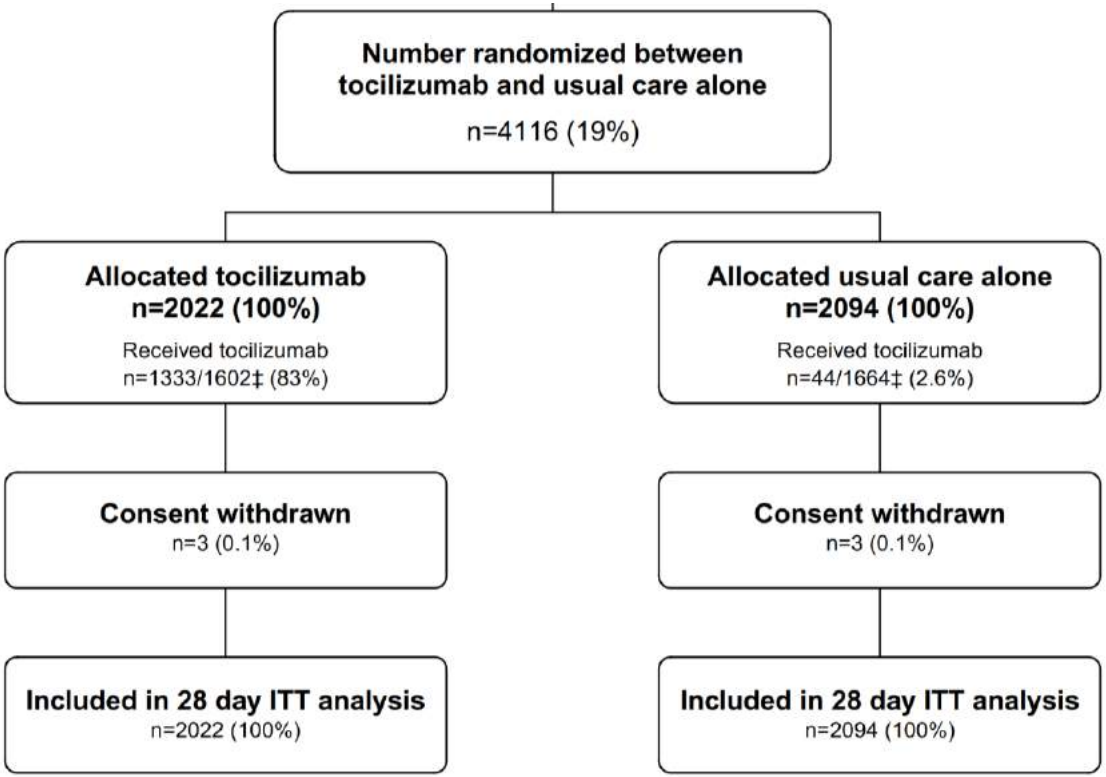


RESULTS_ Baseline characteristic

	Tocilizumab (n=2022)	Usual care (n=2094)
Mean (SD) Age, years	63.3 (13.7)	63.9 (13.6)
≥18 to <70	1332 (66%)	1354 (65%)
≥70 to <80	477 (24%)	480 (23%)
≥80	213 (11%)	260 (12%)
Sex		
Male	1335 (66%)	1437 (69%)
Female*	687 (34%)	657 (31%)
Ethnicity		
White	1356 (67%)	1426 (68%)
Black, Asian, or Minority Ethnic	341 (17%)	357 (17%)
Unknown	325 (16%)	311 (15%)
Number of days since symptom onset	9 (7-13)	10 (7-14)
Number of days since hospitalisation	2 (1-5)	2 (1-5)
Oxygen saturation, %	94 (92-96)	94 (91-95)
Respiratory support at second randomisation		
No ventilator support† low-flow oxygen	935 (46%)	933 (45%)
Non-invasive ventilation‡ High-flow oxygen	819 (41%)	867 (41%)
Invasive mechanical ventilation§	268 (13%)	294 (14%)

	Tocilizumab (n=2022)	Usual care (n=2094)
Biochemistry at second randomisation		
Latest C-reactive protein, mg/L >100 mg/L	143 (107-203)	144 (106-205)
Ferritin, ng/mL >500 ng/mL	947 (497-1599)	944 (507-1533
Creatinine, umol/L	77 (62-98)	77 (62-100)
Previous diseases Risk factor to severe illness		
Diabetes	569 (28%)	600 (29%)
Heart disease	435 (22%)	497 (24%)
Chronic lung disease	473 (23%)	484 (23%)
Tuberculosis	3 (<1%)	5 (<1%)
HIV	7 (<1%)	8 (<1%)
Severe liver disease¶	14 (<1%)	10 (<1%)
Severe kidney impairment|| eGFR<30	118 (6%)	99 (5%)
Any of the above	1100 (54%)	1163 (56%)
SARS-Cov-2 test result		
Positive	1891 (94%)	1967 (94%)
Negative	68 (3%)	66 (3%)
Test result not yet known	63 (3%)	61 (3%)
Use of systemic corticosteroids^ dexamethasone		
Yes	1664 (82%)	1721 (82%)
No	357 (18%)	367 (18%)
Unknown	1 (<1%)	6 (<1%)

RESULTS_ main result

Table 2: Effect of allocation to tocilizumab on main study outcomes

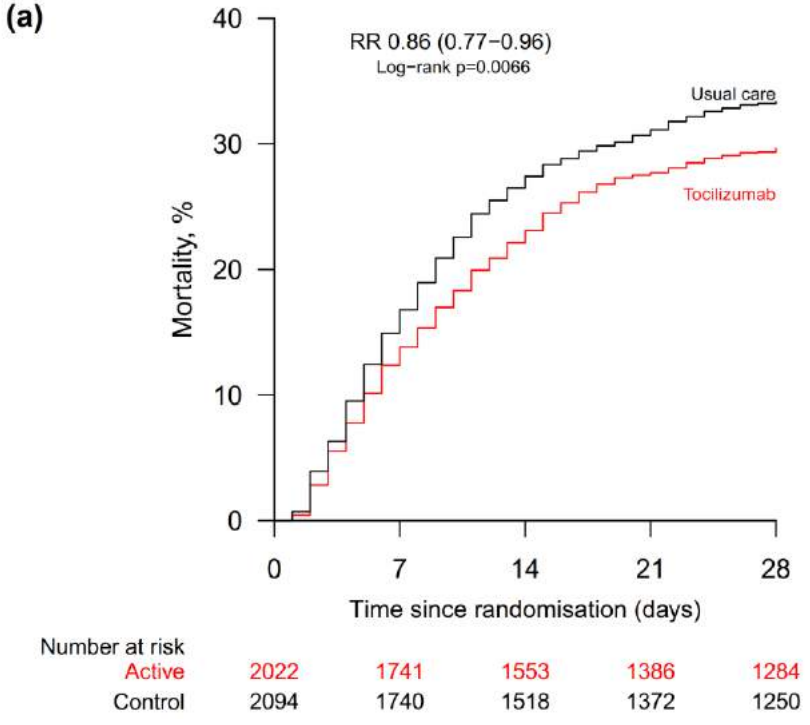
	Treatment allocation			
	Tocilizumab (n=2022)	Usual care (n=2094)	RR (95% CI)	p value
Primary outcome				
Total: 28-day mortality	596 (29%)	694 (33%)	0.86 (0.77-0.96)	0.0066
Secondary outcomes				
Median time to being discharged alive, days	20	>28		
Discharged alive from hospital within 28 days	1093 (54%)	990 (47%)	1.22 (1.12-1.34)	<0.0001
Receipt of invasive mechanical ventilation or death*	571/1754 (33%)	687/1800 (38%)	0.85 (0.78-0.93)	0.0005
Invasive mechanical ventilation	215/1754 (12%)	273/1800 (15%)	0.81 (0.68-0.95)	0.01
Death	471/1754 (27%)	552/1800 (31%)	0.88 (0.79-0.97)	0.01
Subsidiary clinical outcomes				
Receipt of ventilation†	233/935 (25%)	242/933 (26%)	0.96 (0.82-1.12)	0.61
Non-invasive ventilation	222/935 (24%)	223/933 (24%)	0.99 (0.84-1.17)	0.94
Invasive mechanical ventilation	45/935 (5%)	63/933 (7%)	0.71 (0.49-1.03)	0.07
Successful cessation of invasive mechanical ventilation‡	91/268 (34%)	94/294 (32%)	1.07 (0.80-1.43)	0.64
Use of haemodialysis or haemofiltration§	103/2003 (5%)	142/2075 (7%)	0.75 (0.59-0.96)	0.02

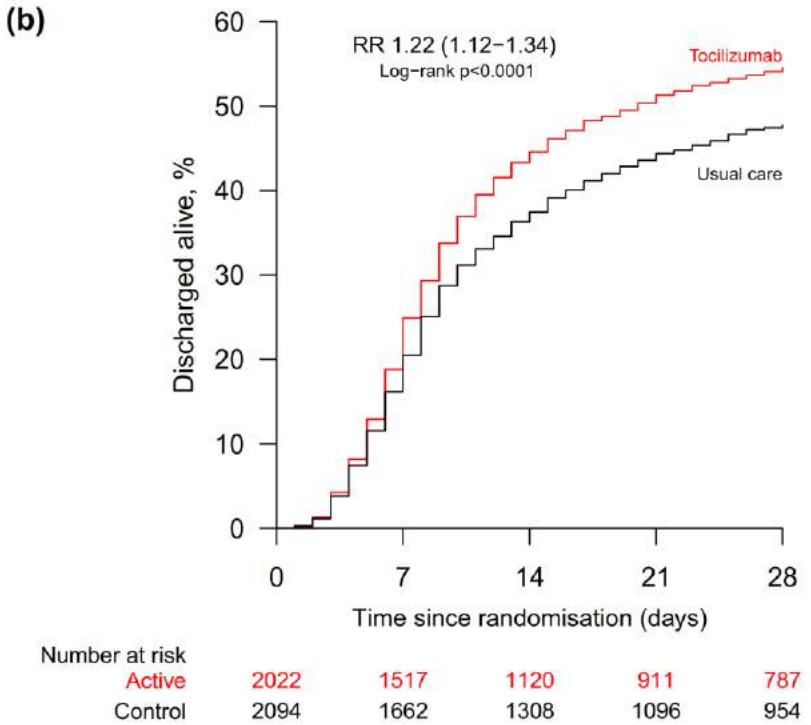
Data are n(%), n/N (%), or median (interquartile range). RR=rate ratio for the outcomes of 28-day mortality, hospital discharge and

使用Tocilizumab可下降14%死亡風險

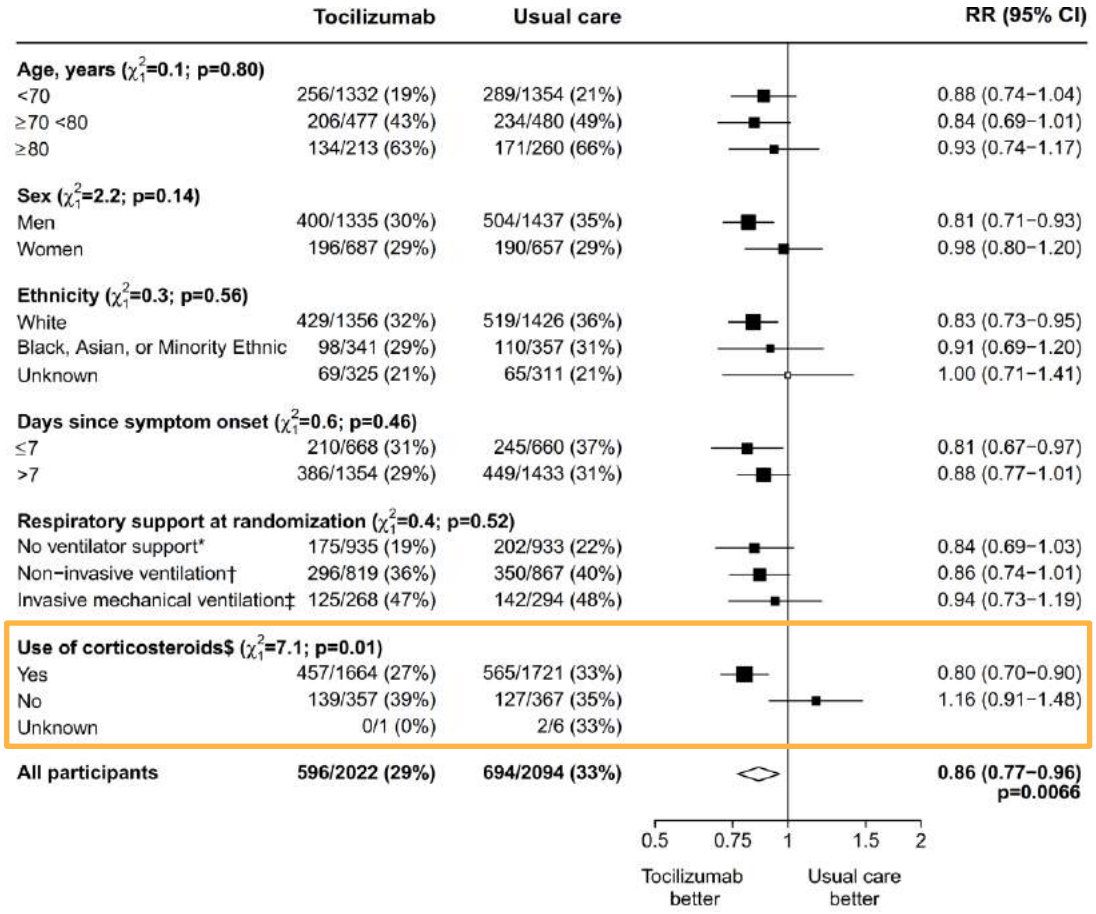
RESULTS_ time to event

- 最快在第二週，CRP降至正常範圍
- 給藥後 3 至 5 天, 嗜中性白血球計數降至曲線之最低點





RESULTS_ Subgroup analysis



Result_ side effect

Cause-specific mortality:

	Treatment allocation		Absolute percent difference (95% CI)
	Tocilizumab (n=2022)	Usual care (n=2094)	
COVID	476 (23.5%)	539 (25.7%)	-2.20 (-4.83,0.43)
Other infection	3 (0.1%)	9 (0.4%)	-0.28 (-0.61,0.05)
Cardiac	1 (0.0%)	1 (0.0%)	0.00 (-0.13,0.14)
Stroke	0 (0.0%)	1 (0.0%)	-0.05 (-0.14,0.05)
Other vascular	1 (0.0%)	3 (0.1%)	-0.09 (-0.28,0.09)
Cancer	6 (0.3%)	3 (0.1%)	0.15 (-0.13,0.44)
Other medical	20 (1.0%)	18 (0.9%)	0.13 (-0.46,0.71)
External	0 (0.0%)	0 (0.0%)	0.00 (0.00,0.00)
Unknown cause*	89 (4.4%)	120 (5.7%)	-1.33 (-2.67,0.01)
All-cause	596 (29.5%)	694 (33.1%)	-3.67 (-6.50,-0.84)

New cardiac arrhythmias: No significant differences

Other serious adverse reaction:

There were **three** reports believed to be related to tocilizumab: all of which resolved with standard treatment.

1 Otitis externa

1 *Staphylococcus aureus* bacteraemia

1 Lung abscess

嚴重副作用: (仿單)

- 嚴重感染的風險性
- 病毒再活化
- 胃腸道穿孔
- 肝臟酵素異常

03

Appraisal

CASP RCT checklist

CASP
Critical Appraisal Skills Programme

Section A: Is the basic study design valid for a randomized controlled trial?
Section B: Was the study methodologically sound?

Section C:
What are the results?

Section D:
Will the results help locally?

Section A:
Is the basic study design valid for a randomized controlled trial?

1. Did the review address a clearly focused question?
   - ✓ Yes
   - Can't tell
   - No
2. Was the assignment of participants to interventions randomized?
   - Yes
   - ✓ Can't tell
   - No
3. Were all participants who entered the study accounted for at its conclusion?
   - Yes
   - ✓ Can't tell
   - No

- **Clear PICO**

- **Central webbased randomisation**
  - Allocation sequence concealed
  - 有些醫院沒有Tocilizumab

- Low loss follow up rate. (0.1%)
- Compliance data available (79%)
- Intention-to-treat analysis

Section B:
Was the study methodologically sound?

4 Were the participants/ investigators/people analyzing outcome ‘blind’?

- Yes
- Can’t tell
- ✓ No

5 Were the study groups similar at the start of the randomized controlled trial

- ✓ Yes
- Can’t tell
- No

6 Did each study group receive the same level of care (that is, were they treated equally)?

- Yes
- Can’t tell
- No

- **Open-label trial**
  - The study still blind to any analyses of aggregated data on study outcomes by treatment allocation.
  - Objective outcome: Mortality
- **Table 1**

Section B:

Was the study methodologically sound?

4 Were the participants/ investigators/people analyzing outcome ‘blind’?

Yes Can’t tell ✓ No

5 Were the study groups similar at the start of the randomized controlled trial

✓ Yes Can’t tell No

6 Did each study group receive the same level of care (that is, were they treated equally)?

✓ Yes Can’t tell No

- **Other treatment:** Randomized 1

	Tocilizumab (n=2022)	Usual care (n=2094)
Compliance data available	1602	1664
Tocilizumab or sarilumab*	1333 (83%)	44 (3%)
Other treatments received		
Lopinavir-ritonavir	47 (3%)	56 (3%)
Corticosteroid	1127 (70%)	1170 (70%)
Hydroxychloroquine	39 (2%)	35 (2%)
Azithromycin or other macrolide	564 (35%)	533 (32%)
Remdesivir	436 (27%)	485 (29%)
Convalescent plasma	328 (20%)	364 (22%)
REGN-COV2	114 (7%)	111 (7%)

- Same follow-up intervals: 28 days

Section C:
What are the results?

7 Were the effects of intervention reported comprehensively?

✓ Yes ○ Can't tell ○ No

8 Was the precision of the estimate of the intervention or treatment effect reported?

✓ Yes ○ Can't tell ○ No

9 Do the benefits of the experimental intervention outweigh the harms and costs?

✓ Yes ○ Can't tell ○ No

- **Power: 4116->3266 patients**
- Mortality rate ratio= 0·86
- 95% confidence interval= 0·77-0·96
- *p*-value=0·007 (P<0.01)
- **NNT:每25人使用，可減少一位病人死亡**
- Subgroup analysis and time to event
- **Harms:**
- No significant differences in the frequency of new cardiac arrhythmias.
- **Cost: 自費 37943元**

Section D:
Will the results help locally?

10 Can the results be applied to the local population?

✓ Yes ○ Can't tell ○ No

11 Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?

✓ Yes ○ Can't tell ○ No

- **<u>There is no ethnic difference in efficacy</u>**
- Asian patients in UK
- Adult (>18 y/o)
- oxygen saturation <92%
- CRP ≥7.5 mg/dL

- 顯著降低住院死亡率
- 顯著降低病人惡化插管與死亡率

04

Discussion

Strengths and limitation

Strengths:

- Randomised
- Large sample size
- Included patients requiring various levels of respiratory support

Limitation:

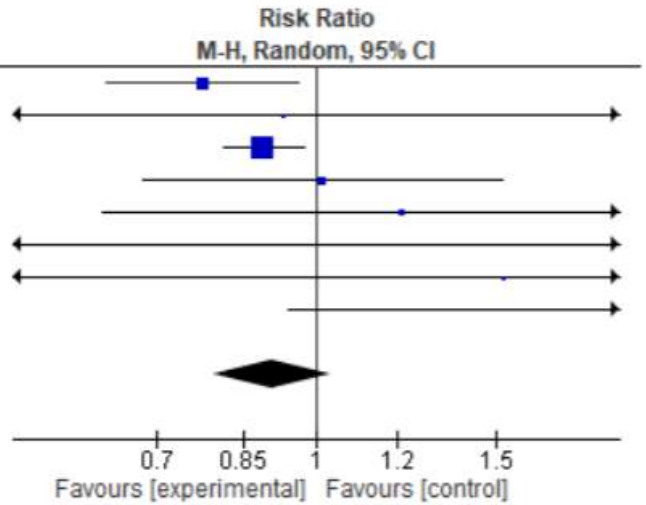
- The primary outcome is available for 92% of patients
- 17% of patients in the tocilizumab group did not receive this treatment
- **Underestimate** of the true effects of actually using the treatment.
- Analyses at **6 months** will provide additional information on the full effects of tocilizumab on clinical outcomes.

RCT of tocilizumab for COVID-19

Figure s4a. Forest plot for the outcome of mortality for tocilizumab vs. no tocilizumab

Study or Subgroup	Tocilizumab Events	Tocilizumab Total	No tocilizumab Events	No tocilizumab Total	Weight	Risk Ratio M-H, Random, 95% CI
Gordon 2021	98	366	142	412	25.4%	0.78 [0.63, 0.96]
Hermine 2020	7	63	8	67	1.9%	0.93 [0.36, 2.42]
Horby 2021	596	2022	694	2094	55.8%	0.89 [0.81, 0.97]
Rosas 2020	58	294	28	144	9.5%	1.01 [0.68, 1.52]
Salama 2020	26	249	11	128	3.8%	1.22 [0.62, 2.38]
Salvarani 2020	2	60	1	63	0.3%	2.10 [0.20, 22.56]
Stone 2020	9	161	3	82	1.1%	1.53 [0.43, 5.49]
Veiga 2021	14	65	6	64	2.2%	2.30 [0.94, 5.61]
Total (95% CI)		**3280**		**3054**	**100.0%**	**0.91 [0.79, 1.04]**
Total events	810		893			

Heterogeneity: Tau² = 0.01; Chi² = 8.32, df = 7 (P = 0.31); I² = 16%
Test for overall effect: Z = 1.43 (P = 0.15)



- Tocilizumab demonstrated a lower relative risk of clinical deterioration, defined as death, need for mechanical ventilation, ECMO, or ICU admission, compared to placebo/usual care RR: 0.83 (0.77, 0.89; **moderate CoE**).
- There is limited safety data in the preliminary report.

IDSA COVID-19 Treatment Guidelines Version 4.1.0 – March 5, 2021

Recommendation 7:
Among hospitalized adults with progressive severe* or critical COVID-19 who have elevated markers of systemic inflammation***, the IDSA guideline panel suggests tocilizumab in addition to standard of care (i.e., steroids) rather than standard of care alone.**
(Conditional recommendation, Low certainty of evidence)

Severity definitions:

*Severe illness is defined as patients with SpO_2 ≤94% on room air, including patients on supplemental oxygen.

**Critical illness is defined as patients on mechanical ventilation and ECMO. Critical illness includes end organ dysfunction as is seen in sepsis/septic shock. In COVID-19, the most commonly reported form of end organ dysfunction is ARDS.

Criterion for systemic inflammation was defined as CRP ≥75 mg/L.

Other Guideline_ not updated yet

2021 WHO COVID-19 Clinical management

15. Therapeutics and COVID-19

For the most up to date clinical practice guideline on therapeutics and COVID-19 see WHO website and BMJ website and MAGICapp.

By 17 December 2020 this guideline contains the following recommendations:

- Strong recommendations against the use of hydroxychloroquine and lopinavir/ritonavir in patients with COVID-19, regardless of disease severity.
- A strong recommendation for systemic corticosteroids in patients with severe and critical COVID-19.
- A conditional recommendation against systemic corticosteroids in patients with non-severe COVID-19.
- A conditional recommendation against remdesivir in hospitalized patients with COVID-19.

台灣2021 新型冠狀病毒(SARS-CoV-2)感染臨床處置暫行指引第九版

Other considerations

The effect of combined use with Remdesivir.

- RECOVERY → no combined use with Remdesivir
- REMAP-CAP → Remdesivir use in 32.8% of patients
- An analysis of 90-day survival showed improved survival in the pooled interleukin-6 receptor antagonist groups, hazard ratio:1.61 (95% CI, 1.25 to 2.08)

Timing to administered

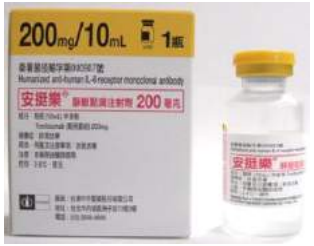
- RECOVERY → Number of days since hospitalization is 48 hours.
- REMAP-CAP → tocilizumab was administered within 24 hours of participants' initiating organ support in an intensive care unit.

Ongoing trial:

- The efficacy of tocilizumab in children with COVID-19
- The efficacy of other IL-6 antagonists in COVID-19: Sarilumab
- The efficacy of different dose of tocilizumab (4 mg/kg vs. 8 mg/kg)

Take home message

Conditional recommendation
Low certainty of evidence



Tocilizumab

適用族群

Severe or critical patients
CRP≥75 mg/L
18歲以上成人
建議同時給予steroid治療

實證療效

可能降低死亡率
延緩臨床症狀的惡
(插管、使用ECMO)

使用時機

越快越好!
<24~48小時內使用

劑量與給予方式

實際體重計算: 8mg/kg (Max:800mg)
使用NaCl 0.9% 100 mL 稀釋
靜脈注射給予(IV)

謝謝聆聽

Q&A

Second stage randomisation (Patients < 1 year of age will NOT be eligible)

Arm	Route	Weight	Dose
No additional treatment	-	-	-
Tocilizumab	Intravenous	Infants < 1 year excluded	
		< 30 kg	12 mg/kg A second dose may be given ≥12 and ≤24 hours later if, in the opinion of the attending clinicians, the patient's condition has not improved.
		≥ 30 kg	8 mg/kg (max 800 mg) A second dose may be given ≥12 and ≤24 hours later if, in the opinion of the attending clinicians, the patient's condition has not improved.
Anakinra	Subcutaneous (Intravenous route if clinically required)	Infants < 1 year or <10 kg excluded	
		≥ 10 kg	2 mg/kg daily for 7 days or discharge whichever is sooner

Practice Changing UpDate on February 2021

Tocilizumab for COVID-19 in Adult and pediatric Grade 2C

For hospitalized adults with COVID-19 who, within the prior 24 to 48 hours, have initiated high-flow supplemental oxygen, non-invasive ventilation, or mechanical ventilation, we suggest adding tocilizumab to usual care (which includes Dexamethasone).

For hospitalized adults with COVID-19 who are receiving low-flow supplemental oxygen. Grade 2C