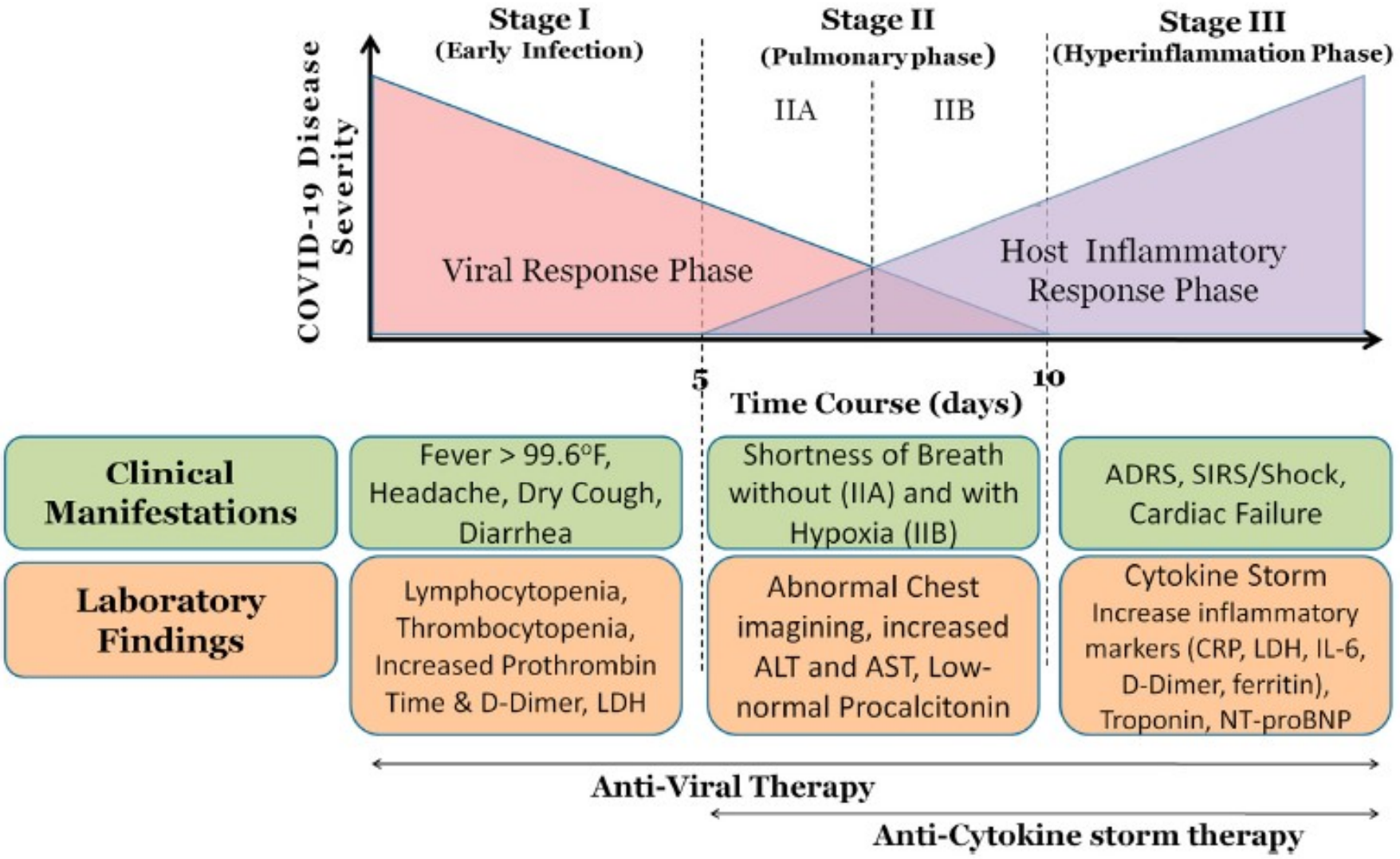
L’anti-interleukine 6 au cours de l’infection par le SARS- CoV-2 : indications en réanimation ?

Pr Jalila BEN KHELIL, Pr Ag Amira JAMOUSSI

- Aucun conflit d’intérêt

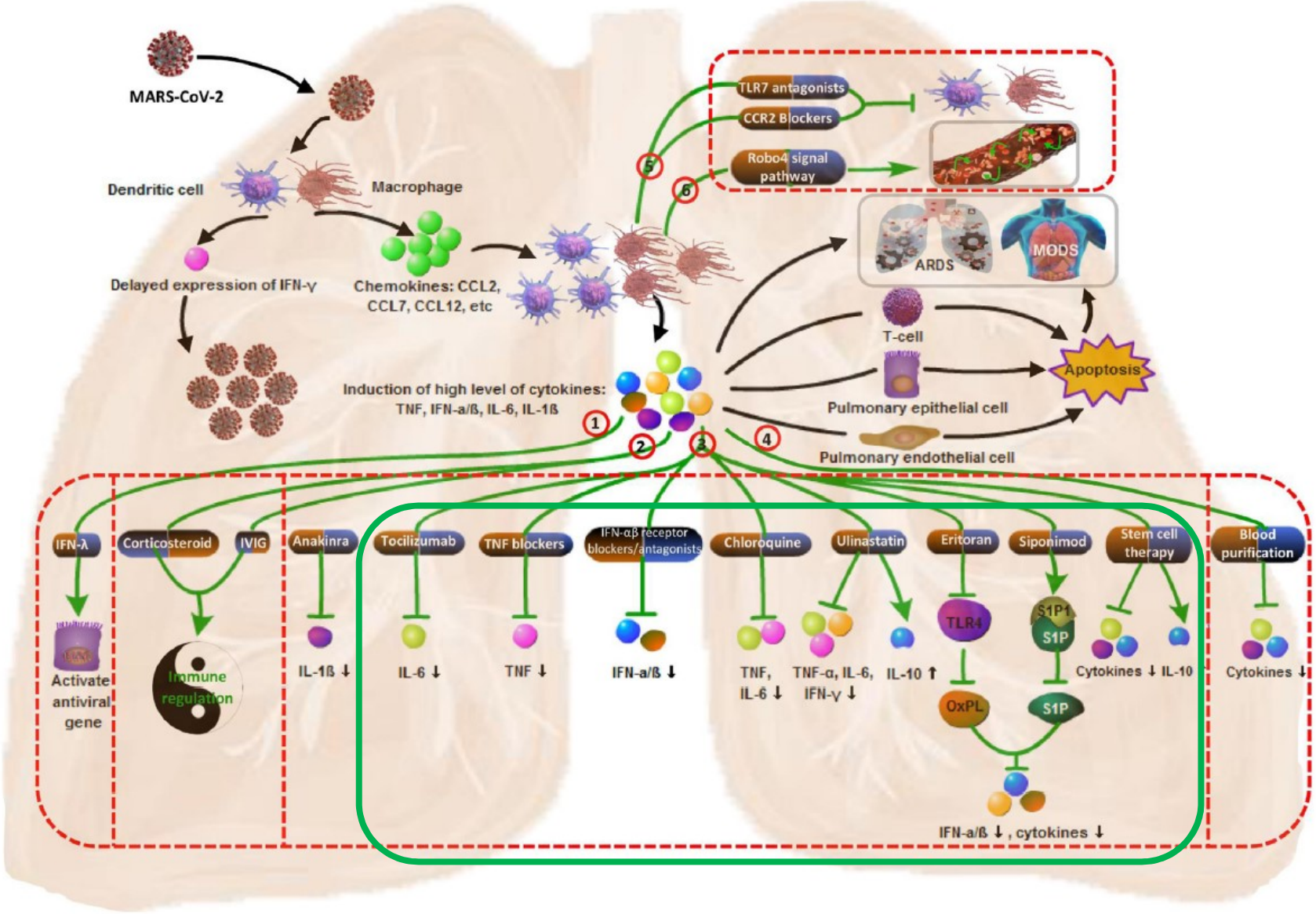
Comment traiter l'infection par le SARS- CoV-2 ??

- 2 possibilités thérapeutiques:
  - Anti-viraux: bloquent la réplication virale
  - Anti-inflammatoires: limitent les lésions induites par la forte inflammation locale



Heliyon 7 (2021) e06158

Mechanism of cytokine storm in COVID-19 and potential therapy.



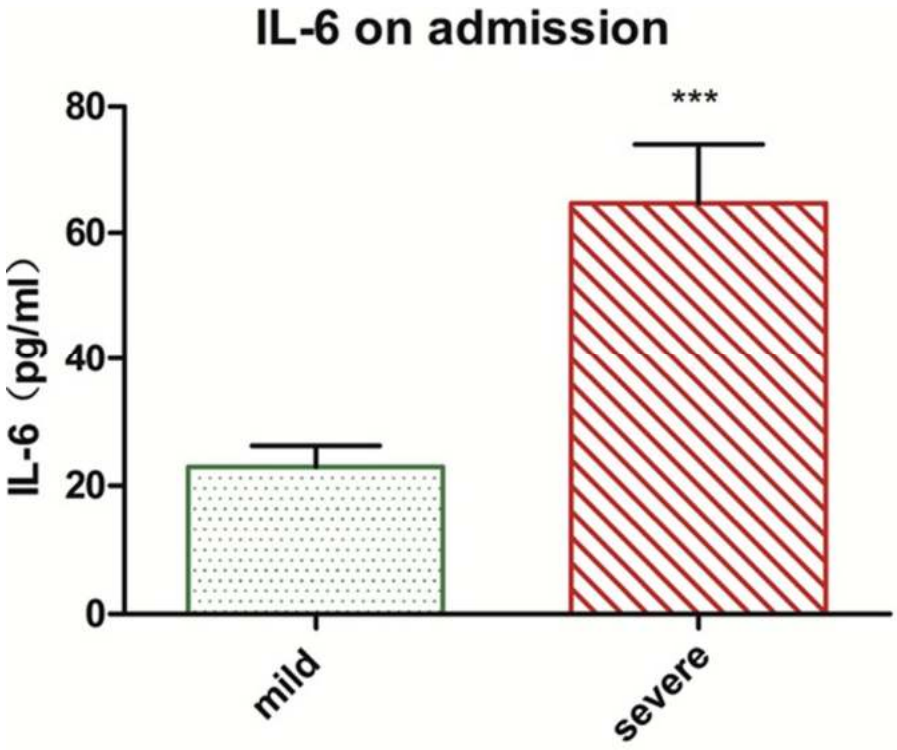
3: Inhibiting the production of cytokines

Q. Ye, B. Wang and J. Mao/Journal of Infection 80 (2020) 607–613

Choix de l'IL-6 ?

- Interleukine 6: médiateur privilégié de l'inflammation (COVID-19)

- COVID-19 sévère ou critique: taux d'IL-6 près de **3 fois** plus élevés que ceux des patients qui ont une maladie modérée.

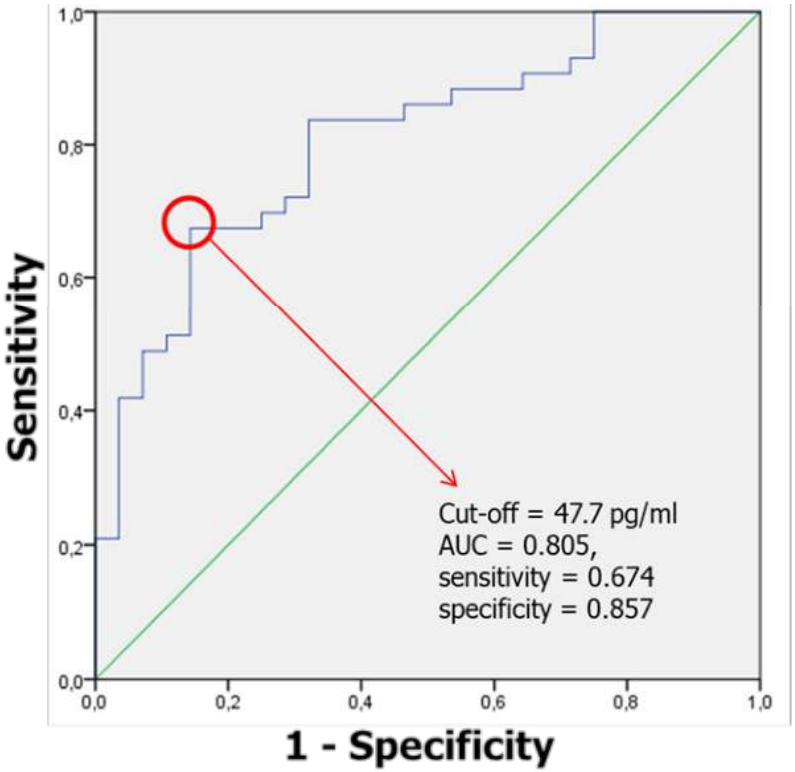


Journal of Clinical Virology 127 (2020) 104370

Choix de l'IL-6 ?

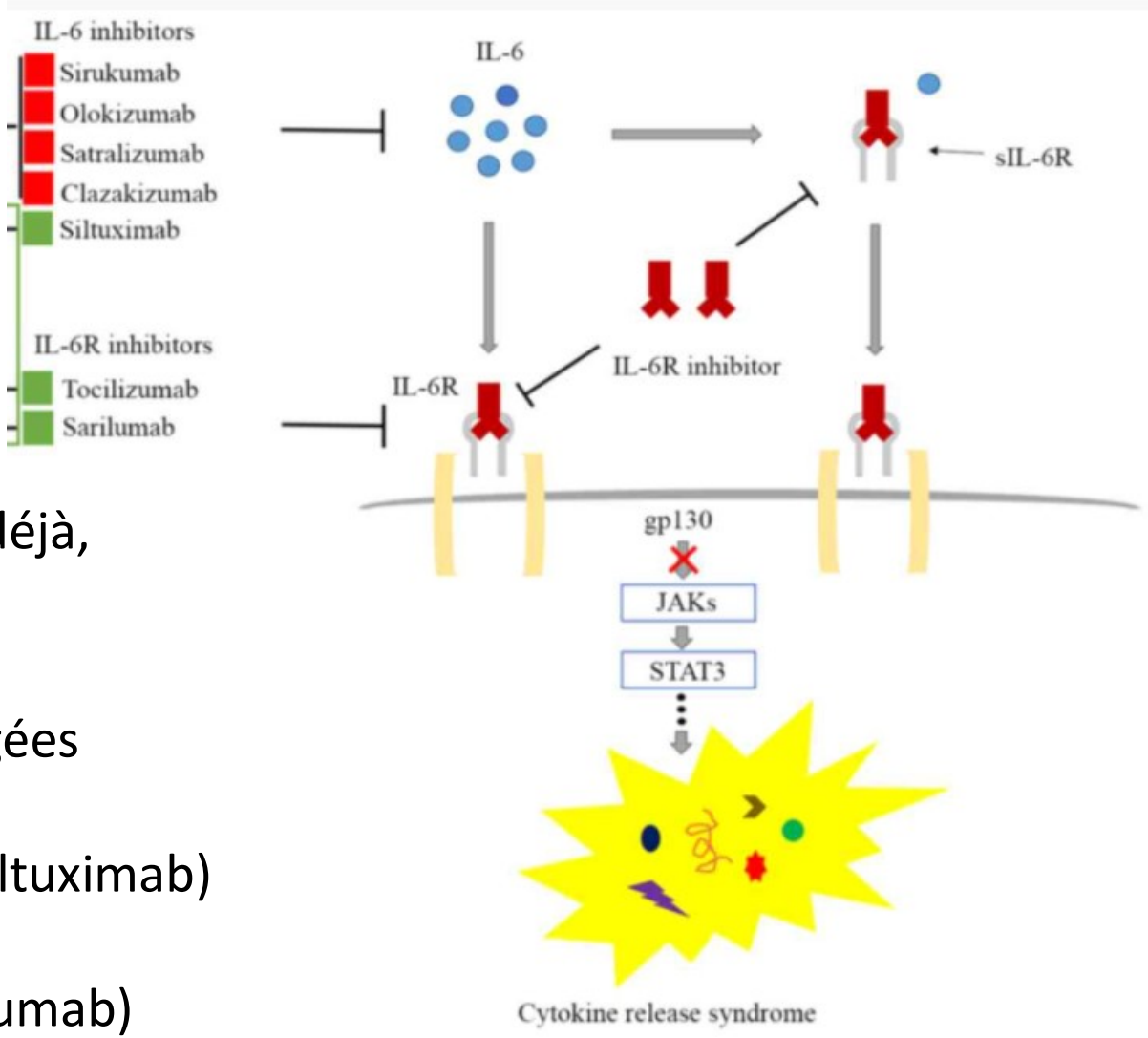
- IL-6 élevés = issues défavorables: admission USI, SDRA et décès.

- Étude personnelle: IL-6 ≥ 47.7 pg/ml facteur prédictif indépendant de mortalité OR 147,9 IC [10,505 – 2083,212] $p < 10^{-3}$



Cytokine 2020;134:155190
International Journal of Infectious Diseases. 2020;95:332-9
Journal of clinical virology. 2020;127:104370

Les anti-IL6



Les anti-IL6 existent déjà, efficacité prouvée

Les biothérapies dirigées contre:

- l'interleukine-6 (siltuximab)
- ou son récepteur (tocilizumab, sarilumab)

Essais cliniques **Anti-IL6**

- 47 Essais cliniques (clinicaltrial.gov)
- 6 Essais cliniques (EU Clinical Trials Register)
- Innombrables acronymes

Essais cliniques **Anti-IL6**

- COVIDSTORM
- COVIDOSE
- HEPMAB
- TOCIVID-19
- ARCHITECTS
- COVIDTOZ
- TOCOVID
- CAVACTA
- EMPACTA
- MARIPOSA
- REMDACTA
- INFLAMMACOV
- CORON-ACT
- TRONCHER
- TOCIBRAS
- TACOS
- TOCIDEX
- CORIMUNO-TOC
- ……

Essais cliniques **Anti-IL6**

Therapeutics and COVID-19

LIVING GUIDELINE
6 JULY 2021

World Health Organization

This WHO *Therapeutics and COVID-19: living guideline* now includes a strong recommendation to use IL-6 receptor blockers (tocilizumab or sarilumab) in patients with severe or critical COVID-19. This guideline update was initiated in response to publication of the RECOVERY *(1)* and REMAP-CAP studies *(2)*. The guideline was finalized when new trial data from REMAP-CAP (1020 patients randomized to direct comparison between tocilizumab and sarilumab) were made available to WHO *(3)*.

ÉCHELLE DE PROGRESSION CLINIQUE		
Échelle ordinale de l'OMS[1]	**Catégorisation**	
	Stade	**Échelon**
1. En communauté, asymptomatique, ARN viral détecté 2. En communauté, symptomatique, sans besoin d'assistance 3. En communauté, symptomatique, besoin d'assistance 4. Hospitalisé, sans besoin d'oxygénation[2] 5. Hospitalisé, état nécessitant une oxygénation par masque ou lunette nasale (O_2+)	Léger	1, 2 ou 3
6. Hospitalisé, état nécessitant une oxygénation nasale à haut débit **OU** une ventilation mécanique non invasive (O_2++) 7. Hospitalisé, état nécessitant une ventilation mécanique invasive ($pO_2/FiO_2 \geq 150$ **OU** $SpO_2/FiO_2 \geq 200$ [O_2+++]) **ET** une intubation	Modéré	4 ou 5
8. Hospitalisé, état nécessitant une ventilation mécanique invasive ($pO_2/FiO_2 < 150$ **OU** $SpO_2/FiO_2 < 200$ [O_2+++]) **OU** un vasopresseur 9. Hospitalisé, état nécessitant une ventilation mécanique invasive ($pO_2/FiO_2 < 150$ [O_2+++]) **ET** un vasopresseur **OU** une dialyse **OU** ECMO 10. Mort	Sévère à critique	6, 7, 8, ou 9

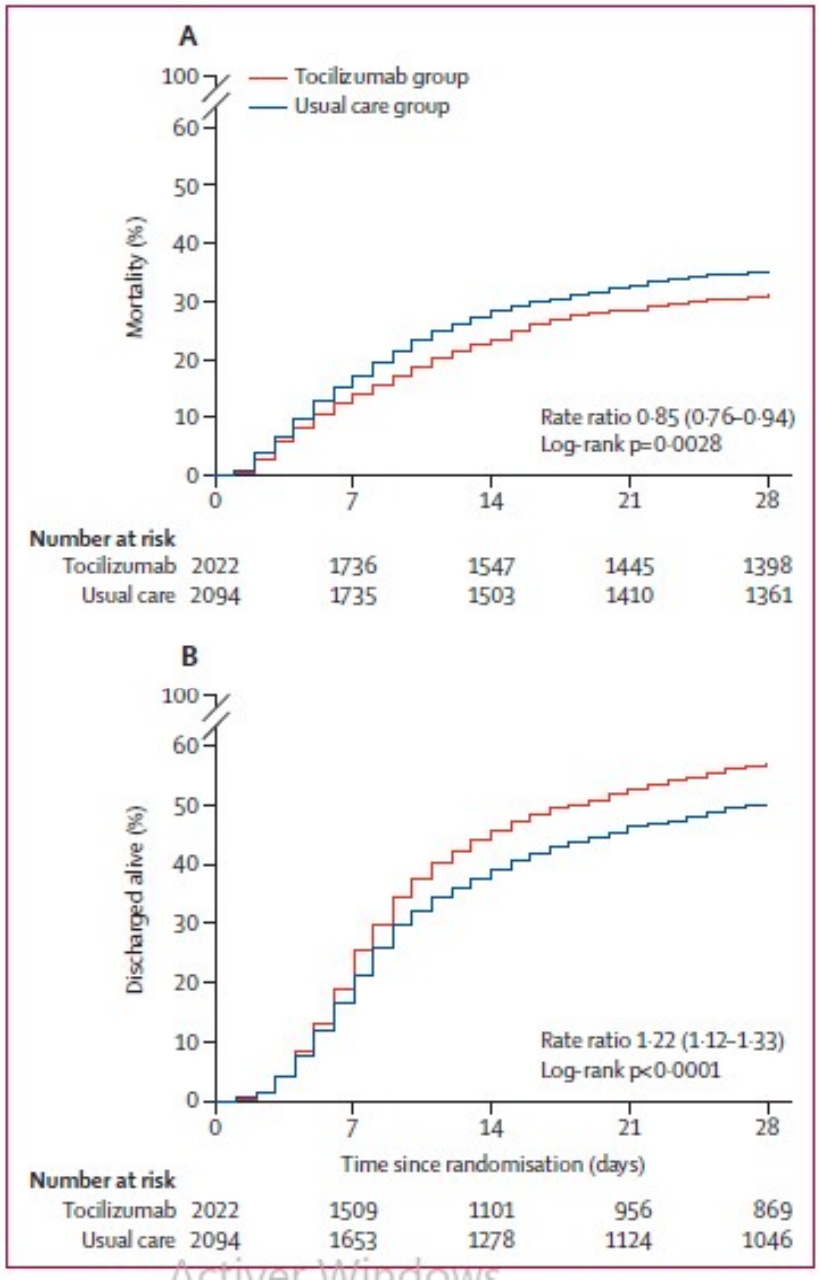
1. *WHO Working Group. A minimal common outcome measure set for COVID-19 clinical research. The Lancet Infectious diseases 2020;20(8):e192-e7.*

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

RECOVERY Collaborative Group*

Lancet 2021; 397: 1637–45

- Randomisé, contrôlé
- SpO_2< 92% AA ou sous O_2 + CRP > 75 mg/dl
- SOC + Tocilizumab VS SOC
- 2ème dose (12 à 24 h) si pas d'amélioration
- N=4119 patients
- Mortalité 31% VS 35 %, p=0,0028



Lancet 2021; 397: 1637–45

- 9 patients sans O2
- 1859 patients: faible débit O2
- 82 % des patients sous CPAP, HFNC ou VNI ont eu des corticoides

	Tocilizumab group (n=2022)	Usual care group (n=2094)
Respiratory support at second randomisation		
No ventilator support†	935 (46%)	933 (45%)
Non-invasive ventilation‡	819 (41%)	867 (41%)
Invasive mechanical ventilation§	268 (13%)	294 (14%)

Lancet 2021; 397: 1637–45

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19

The REMAP-CAP Investigators*

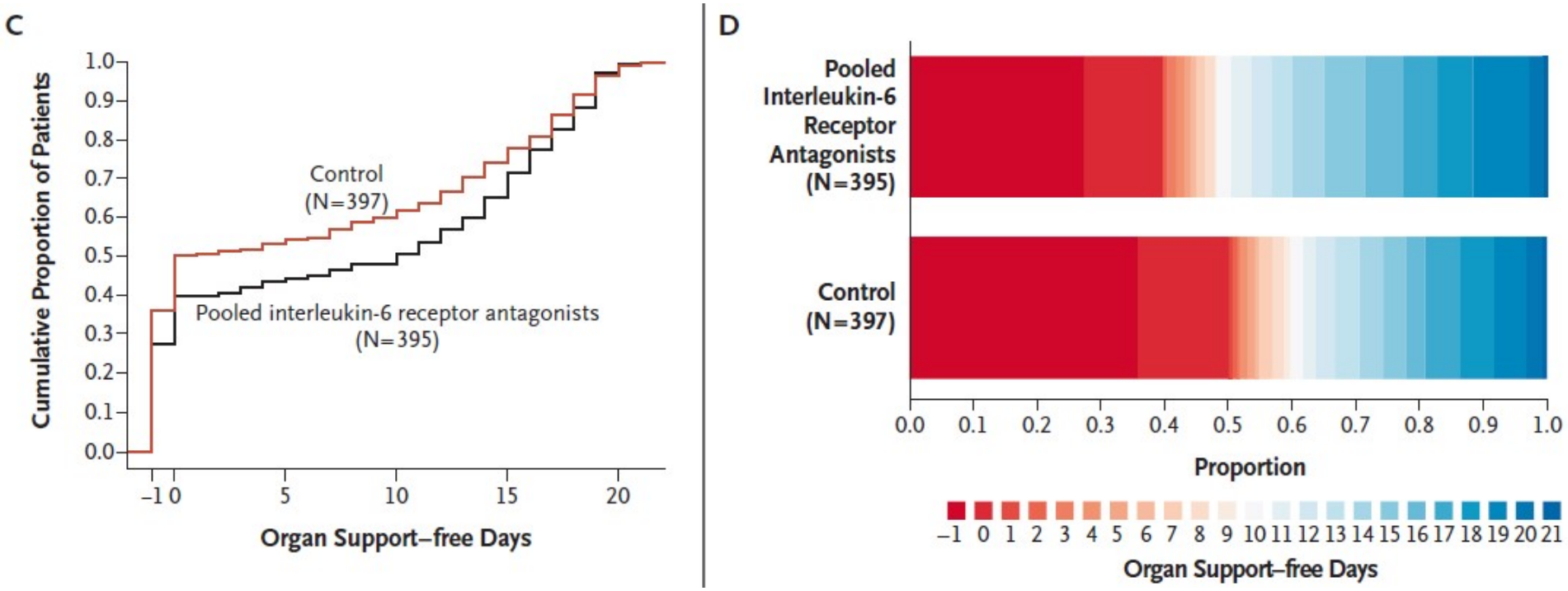
- Adultes, ICU, COVID sévère
- Randomisés 24h après le début du support d'organe
  - VM: OHD (D > 30L/mn et FiO2 > 40%)/VNI/VI
  - Vasopresseurs
- Bras anti-IL6 (tocilizumab ou sarilumab) vs placebo

Méthodologie complexe

- Critère de jugement: Nombre de jours libres de support d'organe (respiratoire ou cardio-vasculaire) jusqu'à J21
- Critère composite, échelle ordinale
- Décès = -1/ survivants (nombre de jours free)
- Une cotation élevée est synonyme de guérison plus rapide
- FDA: 1,5 jours= différence significative

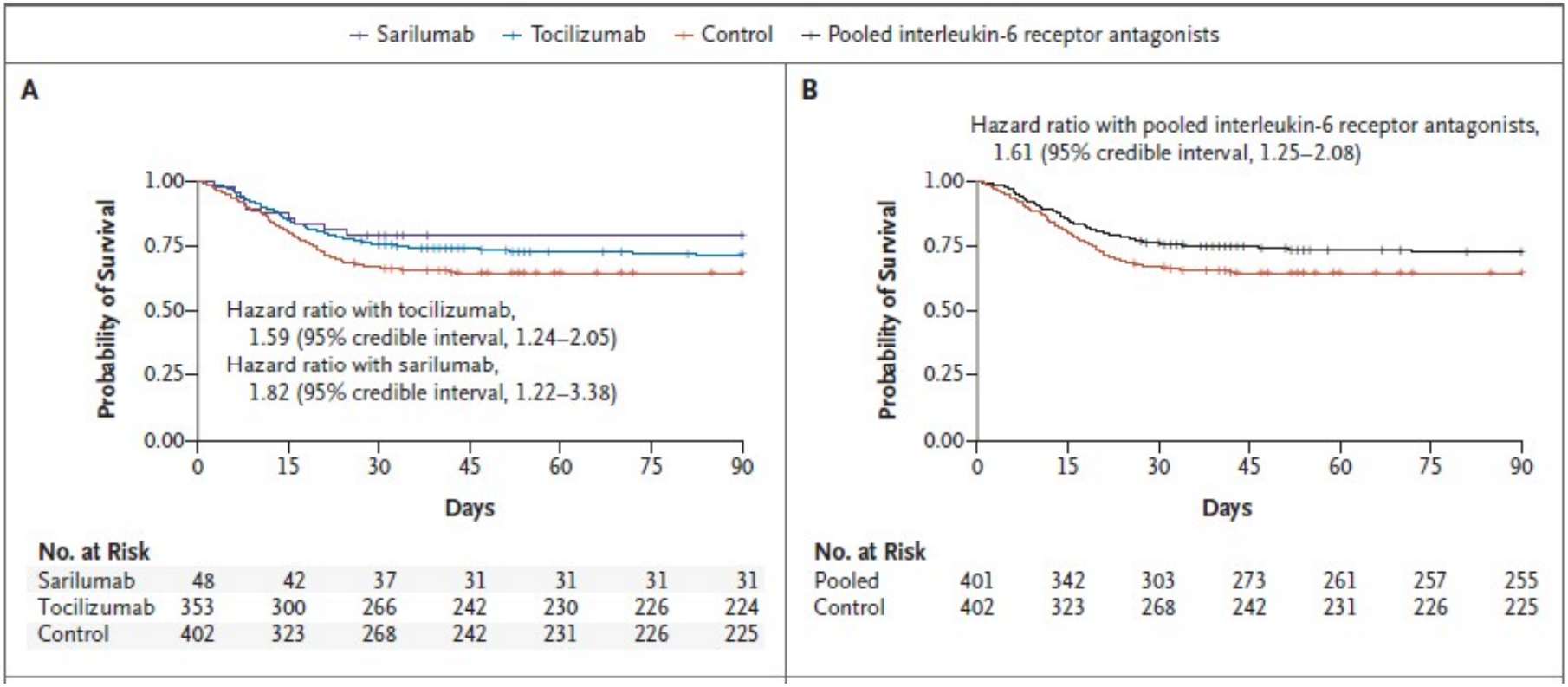
Table 2. Primary and Secondary Outcomes.*

Outcome or Analysis	Tocilizumab (N=353)	Sarilumab (N=48)	Control (N=402)
Primary outcome			
Organ support–free days			
Median (IQR)	10 (–1 to 16)	11 (0 to 16)	0 (–1 to 15)
Adjusted odds ratio			
Mean	1.65±0.23	1.83±0.44	1
Median (95% credible interval)	1.64 (1.25 to 2.14)	1.76 (1.17 to 2.91)	1
Probability of superiority to control — %	>99.9	99.5	—



This article was published on February 25, 2021, at NEJM.org.

DOI: 10.1056/NEJMoa2100433


Sarilumab
Tocilizumab
Control
Pooled interleukin-6 receptor antagonists
A
Probability of Survival
1.00
0.75
0.50
0.25
0.00
Hazard ratio with tocilizumab,
1.59 (95% credible interval, 1.24–2.05)
Hazard ratio with sarilumab,
1.82 (95% credible interval, 1.22–3.38)
0
15
30
45
60
75
90
Days
No. at Risk
Sarilumab 48 42 37 31 31 31 31
Tocilizumab 353 300 266 242 230 226 224
Control 402 323 268 242 231 226 225
B
Hazard ratio with pooled interleukin-6 receptor antagonists,
1.61 (95% credible interval, 1.25–2.08)
Probability of Survival
1.00
0.75
0.50
0.25
0.00
0
15
30
45
60
75
90
Days
No. at Risk
Pooled 401 342 303 273 261 257 255
Control 402 323 268 242 231 226 225

Google Scholar

The REMAP-CAP Investigators Interleukin-6 receptor antagonists in criticall

Articles

Date indifférente
Depuis 2021
Depuis 2020
Depuis 2017
Période spécifique...

Trier par pertinence
Trier par date

[HTML] **Interleukin-6 receptor antagonists** in **critically ill patients** with **Covid-19**.

AC Gordon, PR Mouncey, F Al-Beidh... - ... **New England journal** ..., **2021** - europepmc.org

Background The efficacy of interleukin-6 receptor antagonists in critically ill patients with coronavirus disease 2019 (Covid-19) is unclear. Methods We evaluated tocilizumab and sarilumab in an ongoing international, multifactorial, adaptive platform trial. Adult patients with Covid-19, within 24 hours after starting organ support in the intensive care unit (ICU), were randomly assigned to receive tocilizumab (8 mg per kilogram of body weight), sarilumab (400 mg), or standard care (control). The primary outcome was respiratory and ...

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

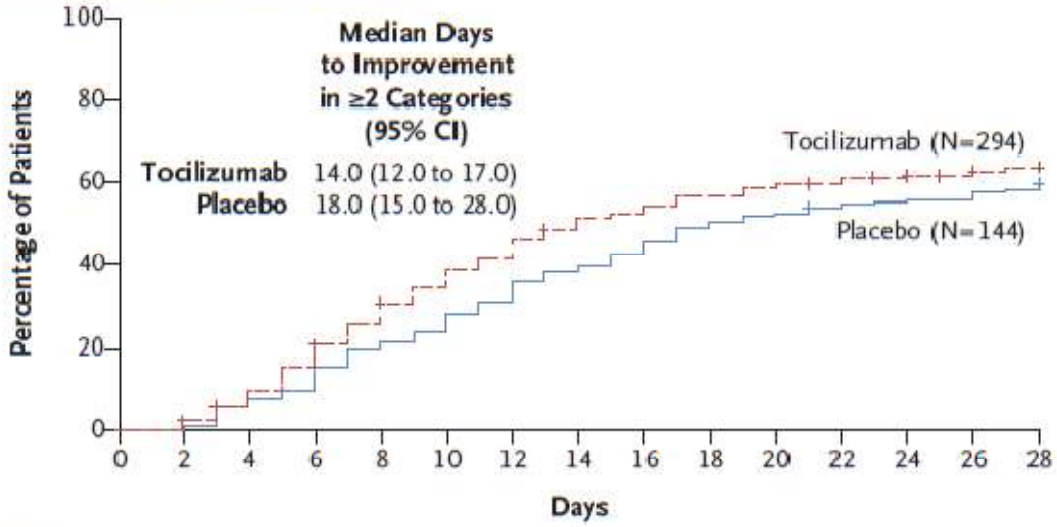
Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia

I.O. Rosas, N. Bräu, M. Waters, R.C. Go, B.D. Hunter, S. Bhagani, D. Skiest, M.S. Aziz, N. Cooper, I.S. Douglas, S. Savic, T. Youngstein, L. Del Sorbo, A. Cubillo Gracian, D.J. De La Zerda, A. Ustianowski, M. Bao, S. Dimonaco, E. Graham, B. Matharu, H. Spotswood, L. Tsai, and A. Malhotra

- Essai phase 3, COVID sévère
- Randomisation 2:1 tociluzimab 8mg/kg vs palcebo
- 2ème dose, 8 à 24 h, (1/4 des patients)
- Primary outcome: état clinique à J28 évalué par une échelle ordinale:
  - 1= sortant ou prêt à la sortie
  - 7= décès
- Tociluzimab (n=294) vs placebo (n= 144)

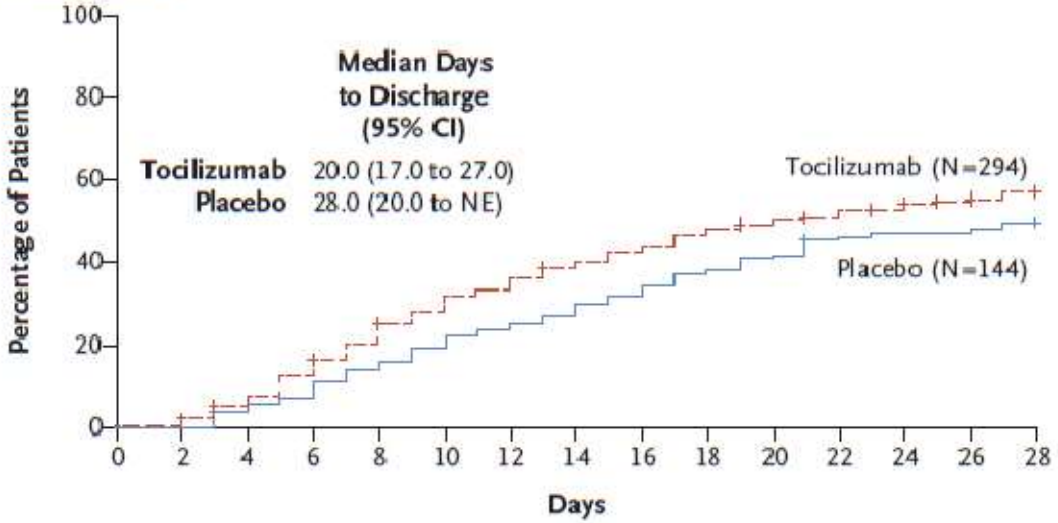
N Engl J Med 2021;384:1503-16.
DOI: 10.1056/NEJMoa2028700

A Improvement in Ordinal Clinical Status



No. at Risk															
Tocilizumab	294	294	275	248	216	189	169	148	137	124	118	115	110	107	99
Placebo	144	144	135	130	115	109	99	88	82	73	69	65	63	62	59

B Hospital Discharge



No. at Risk															
Tocilizumab	294	294	276	255	231	208	192	176	165	153	145	139	132	124	114
Placebo	144	144	138	133	123	115	109	104	97	90	84	76	74	74	70

N Engl J Med 2021;384:1503-16.
DOI: 10.1056/NEJMoa2028700

Table 2. Primary and Secondary Efficacy Outcomes.*

Outcome	Tocilizumab (N=294)	Placebo (N=144)	Difference or Hazard Ratio (95% CI)	P Value
Primary outcome				
Median value for clinical status on 7-category ordinal scale at day 28 (95% CI)	1.0 (1.0 to 1.0)	2.0 (1.0 to 4.0)	−1.0 (−2.5 to 0.0)	0.31†
Secondary outcomes				
Median value for clinical status at day 14 on 7-category ordinal scale (95% CI)‡	3.0 (2.0 to 4.0)	4.0 (3.0 to 5.0)	−1.0 (−2.0 to 0.5)	
Death at day 28 — no. (%)	58 (19.7)	28 (19.4)	0.3 (−7.6 to 8.2)§	0.94
Median no. of days until hospital discharge or readiness for discharge (95% CI)	20.0 (17.0 to 27.0)	28.0 (20.0 to NE)	1.35 (1.02 to 1.79)¶	

In this randomized trial involving hospitalized patients with severe Covid-19 pneumonia, the use of tocilizumab did not result in significantly better clinical status or lower mortality than placebo at 28 days. (Funded by F. Hoffmann–La Roche and the Department of Health and Human Services; COVACTA ClinicalTrials.gov number, NCT04320615.)

N Engl J Med 2021;384:1503-16.
DOI: 10.1056/NEJMoa2028700

Femmes enceintes ?

- Peu de données (COVID)
- Femmes enceintes et allaitantes souvent exclues des études
- Enjeu éthique, pronostic maternel prime

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Narrative review

Tocilizumab for coronavirus disease 2019 in pregnancy and lactation: a narrative review

- 610 patientes dont 20 COVID
- Avortements spontanés (21,7 % vs 15 %)
- Accouchements prématurés (31 % vs 10 %)
- Malformations congénitales (4,5 % vs 3 %)
- Facteurs confondants (méthotrexate, COVID)

Clinical Microbiology and Infection
doi.org/10.1016/j.cmi.2021.08.016

Enfants ?

- Indications exceptionnelles

Caring for Critically Ill Children With Suspected or Proven Coronavirus Disease 2019 Infection: Recommendations by the Scientific Sections' Collaborative of the European Society of Pediatric and Neonatal Intensive Care*

Pediatric Critical Care Medicine

Enfants instables avec MIS-C si IL-6 élevé, hyperferritinémie, thrombocytémie, EC

Review

COVID-19 Management in the Pediatric Age: Consensus Document of the COVID-19 Working Group in Paediatrics of the Emilia-Romagna Region (RE-CO-Ped), Italy

Int. J. Environ. Res. Public Health 2021

Non recommandé

American College of Rheumatology Clinical Guidance for Pediatric Patients with Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARS-CoV-2 and Hyperinflammation in COVID-19. Version 2.

Non recommandé

- 1ère dose= 4–8 mg/kg.
- Dose recommandée COVID: 8 mg/kg , max 800 mg
- Dose additionnelle 8 à 12 h (Alattar et al, 2020), même dose, maximum de 2 doses cumulatives.

JOURNAL OF MEDICAL VIROLOGY WILEY

J Med Virol. 2020;92:2042-2049.

MODALITÉS D'USAGE

Médicament	Posologie	Durée du traitement	Perfusion[3]
CHOIX À PRIVILÉGIER			
Tocilizumab[1]	> 30 kg et ≤ 40 kg : 8 mg/kg[2] > 40 kg et ≤ 65 kg : 400 mg > 65 et ≤ 90 kg : 600 mg > 90 kg : 800 mg Autre posologie : 8 mg/kg (max. 800 mg)	Injection unique[8]	Dilution[4] dans 100 ml de NaCl 0,9 % Durée : 60 minutes[5]
	< 30 kg : 12 mg/kg[2]	Injection unique[8]	Dilution[4] dans 50 ml de NaCl 0,9 % Durée : 60 minutes[5]
OPTION ALTERNATIVE[6] sauf pour les patients en oxygénothérapie à faible débit (échelon 5)			
Sarilumab[1,6,7]	> 40 kg : 400 mg	Injection unique[8]	Dilution[4] dans 100 ml de NaCl 0,9 % Durée : 60 minutes[5]

Notre expérience

- Molécule onéreuse, 6 MD / patient, pas d'AMM
- 2 groupes mached, appariement selon: age, genre, severité du SDRA et % d'atteinte au CT.

	Tocilizumab +dexamethasone n=40	**Dexamethasone n=40**	**p**
IMV, n (%)	23 (52)	21(48)	0.653
Death, n (%)	23(57)	17(42)	0.180
LOS in ICU, median [IQR]	8 [5-14]	8.5 [6-12]	0.312
Pulmonary embolism, n(%)	3(7,5)	10(25)	0,034

Therapeutics and COVID-19

LIVING GUIDELINE
6 JULY 2021

World Health Organization

8. Uncertainties, emerging evidence and future research

*IL-6 receptor blockers (*despite the strong recommendation, there are a number of uncertainties that persist):

- long-term mortality and functional outcomes in COVID-19 survivors;
- safety data in terms of nosocomial infections
- data in children, pregnant patients and those that are already immunocompromised
- patients with non-severe COVID-19
- immunity and the risk of a subsequent infection, which may impact the risk of death after 28 days;
- outcomes by different IL-6 receptor blocker dosing and optimal timing of drug initiation.

Trials en cours ?

NIH U.S. National Library of Medicine
ClinicalTrials.gov

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Status	Study Title	Conditions	Interventions	Locations
Recruiting	EFFICACY and SAFETY OF BEVACIZUMAB (ZIRABEV®) IN PATIENTS WITH SEVERE HYPOXEMIC COVID-19	• Corona Virus Infection • SARS (Severe Acute Respiratory Syndrome) • Virus Diseases • (and 5 more...)	• Drug: BEVA+SOC • Drug: SOC	• Hôpital TENON Paris, France

Arms and Interventions

Go to

Arm	Intervention/treatment
Experimental: Bevacizumab + SOC Bevacizumab : 7.5 mg / kg (with a maximum of 750 mg) on day 1 (D1) SOC : patients will receive the best of standard of care including corticosteroids, anticoagulant, antibiotics and **tociluzimab**	Drug: BEVA+SOC Bevacizumab : 7.5 mg / kg (with a maximum of 750 mg) on day 1 (D1) SOC : patients will receive the best of standard of care including corticosteroids, anticoagulant, antibiotics and **tociluzimab**
Active Comparator: SOC SOC : patients will receive the best of standard of care including corticosteroids, anticoagulant, antibiotics and **tociluzimab**	Drug: SOC patients will receive the best of standard of care including corticosteroids, anticoagulant, antibiotics and **tociluzimab**

Quel avenir pour les **Anti-IL6 ?**

- Tocilizumab serum concentration in COVID-19 patients

Reference	Study design	Patients	MoA/dose	TCZ Serum level	Kit/technique	Key results
Moes D.J.A.R et al. 2021 (Netherlands)	Open-label, observational pharmacokinetic and pharmacodynamic evaluation study	29 patients 18 years or older ICU admitted COVID-19	8 mg/kg TCZ with a max of 800 mg	$AUC_{0\text{-inf 1st DOSE}}$: 938 [±190] ug/mL* days At 15 days > 1 ug/ml	Validated ELISA-method	Fixed dosing of 600 mg tocilizumab is a cost saving, logistically attractive and safe alternative without losing efficacy
Boone et al. 2021 (Netherlands)	Prospective pharmacokinetic study	COVID-19-associated cytokine storm syndrome (CSS)	8mg/kg, max. 800mg) single infusion	> 1 µg/ml	Validated ELISA-method	Clearance of TCZ is faster compared to RA-patients at steady state. Single dose of tocilizumab in CSS-patients is enough to cover IL-6 mediated hyperinflammation

TAKE HOME MESSAGES

- Anti-IL6: COVID sévère à critique
- Zones d’incertitude
- Question résolue ??