COVID-19
ONLINE EDUCATIONAL PROGRAM

# Shelter from the storm? Reassessing the Role of Tocilizumab in COVID-19 Pneumonia


## Jonathan Parr, MD, MPH

*University of North Carolina School of Medicine, United States*


academic medical education

# Disclosures

**Competing interests**

- I receive research support from the World Health Organization and Gilead Sciences and in-kind support from Abbott Diagnostics. None of these are related to COVID-19.

**Off-label use of therapeutics**

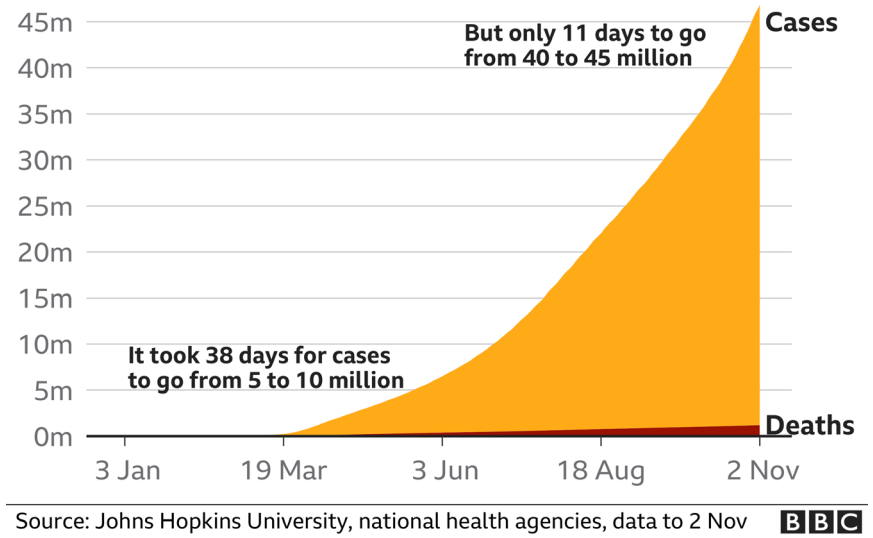
- Tocilizumab and other immunomodulatory agents discussed are **not** FDA approved for COVID-19.

# Where are we going?

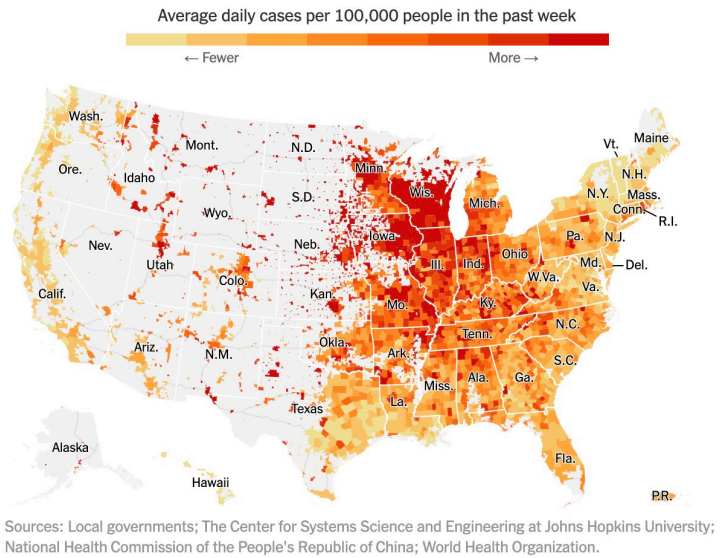
1. COVID-19 and ‘cytokine storm’
2. Tocilizumab: what is the evidence?
3. Lessons learned
   - Targeted immunomodulators
   - Weighing the evidence (or, guzzling from the COVID-19 firehose)

# No rest for the weary

**Global**




**US**





https://www.bbc.com/news/world-51235105; https://www.nytimes.com/interactive/2020/world/coronavirus-maps.html

# Why do some patients deteriorate so quickly?

**An Interferon-γ-Related Cytokine Storm in SARS Patients**

Kao-Jean Huang,[1] Ih-Jen Su,[2,3] Michel Theron,[1] Yi-Chun Wu,[2] Shu-Kuan Lai,[2] Ching-Chuan Liu,[1] and Huan-Yao Lei[1]*

[1]*Departments of Basic Medicine, Microbiology and Immunology, College of Medicine, National Cheng Kung University, Tainan, Taiwan*
[2]*Center for Disease Control, Department of Health, Taipei, Taiwan*
[3]*Division of Clinical Research, National Health of Research Institute, Tainan, Taiwan*

- Hyperinflammatory state observed in SARS-CoV-1 & 2
- 'Cytokine storm' used to describe elevated cytokine and chemokines (compared to normal) in SARS-CoV-1
- **Cytokine storm paradigm** rapidly adopted early in the COVID-19 pandemic.
- IL-6 elevation associated with death & severe disease

**Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study**

*Fei Zhou*, Ting Yu*, Ronghui Du*, Guohui Fan*, Ying Liu*, Zhibo Liu*, Jie Xiang*, Yeming Wang, Bin Song, Xiaoying Gu, Lulu Guan, Yuan We*
*Hui Li, Xudong Wu, Jiuyang Xu, Shengjin Tu, Yi Zhang, H*

JAMA Internal Medicine | Original Investigation

**Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China**

Chaomin Wu, MD; Xiaoyan Chen, MD; Yanping Cai, MD; Jia'an Xia, MD; Xing Zhou, MD; Sha Xu, MD; Hanping Huang, MD; Li Zhang, MD; Xia Zhou, MD; Chunling Du, MD; Yuye Zhang, BD; Juan Song, BD; Sijiao Wang, BD; Yencheng Chao, MD; Zeyong Yang, MD; Jie Xu, MD; Xin Zhou, MD; Dechang Chen, MD; Weining Xiong, MD; Lei Xu, MD; Feng Zhou, MD; Jinjun Jiang, MD; Chunxue Bai, MD; Junhua Zheng, MD; Yuanlin Song, MD

*Clinical Infectious Diseases*

MAJOR ARTICLE

**Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China**

Chuan Qin,[1,a] Luoqi Zhou,[1,a] Ziwei Hu,[1] Shuoqi Zhang,[2] Sheng Yang,[1] Yu Tao MD,[3] Cuihong Xie,[4] Ke Ma,[5] Ke Shang,[1] Wei Wang,[1] and Dai-Shi Tian[1]

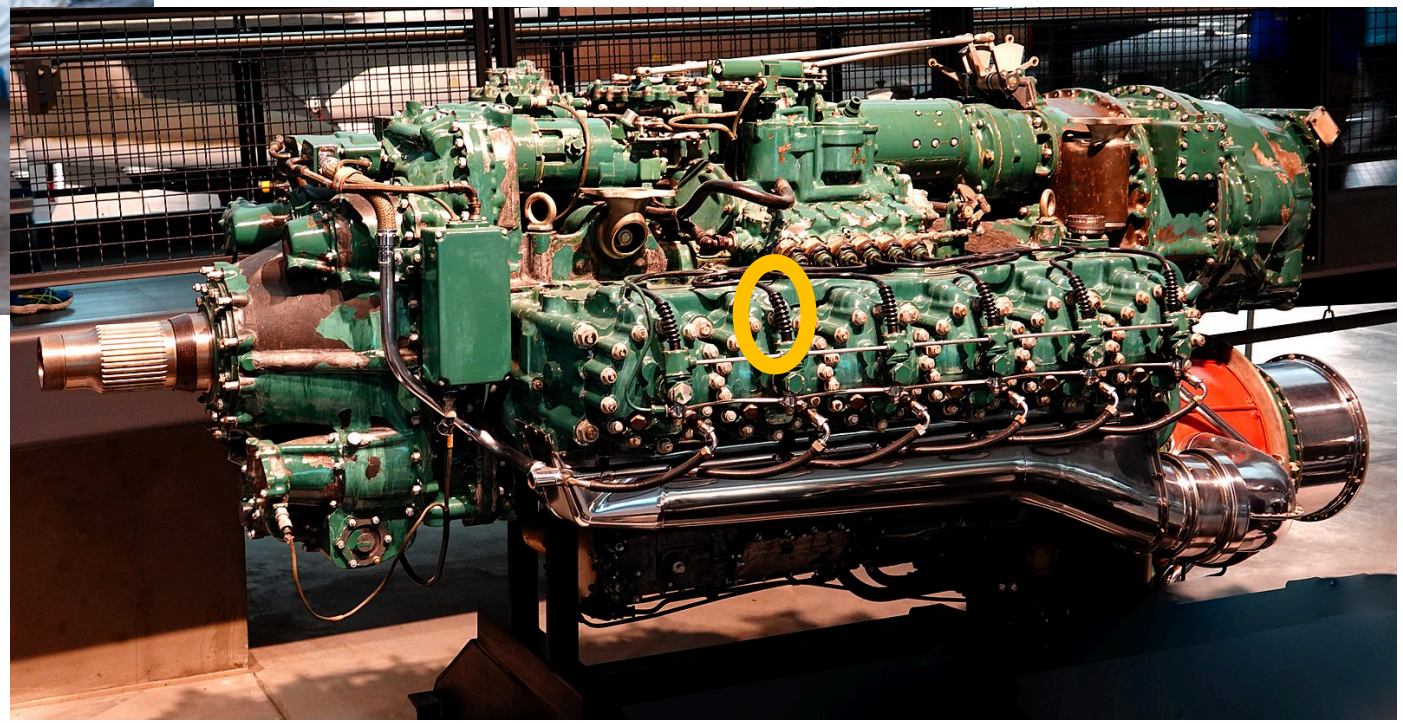
Huang K-J J Med Virol 2005; Zhou Lancet 2020; Qin Clin Infect Dis 2020; Wu JAMA Int Med 2020

# Hyperinflammation in COVID-19 – should we intervene?

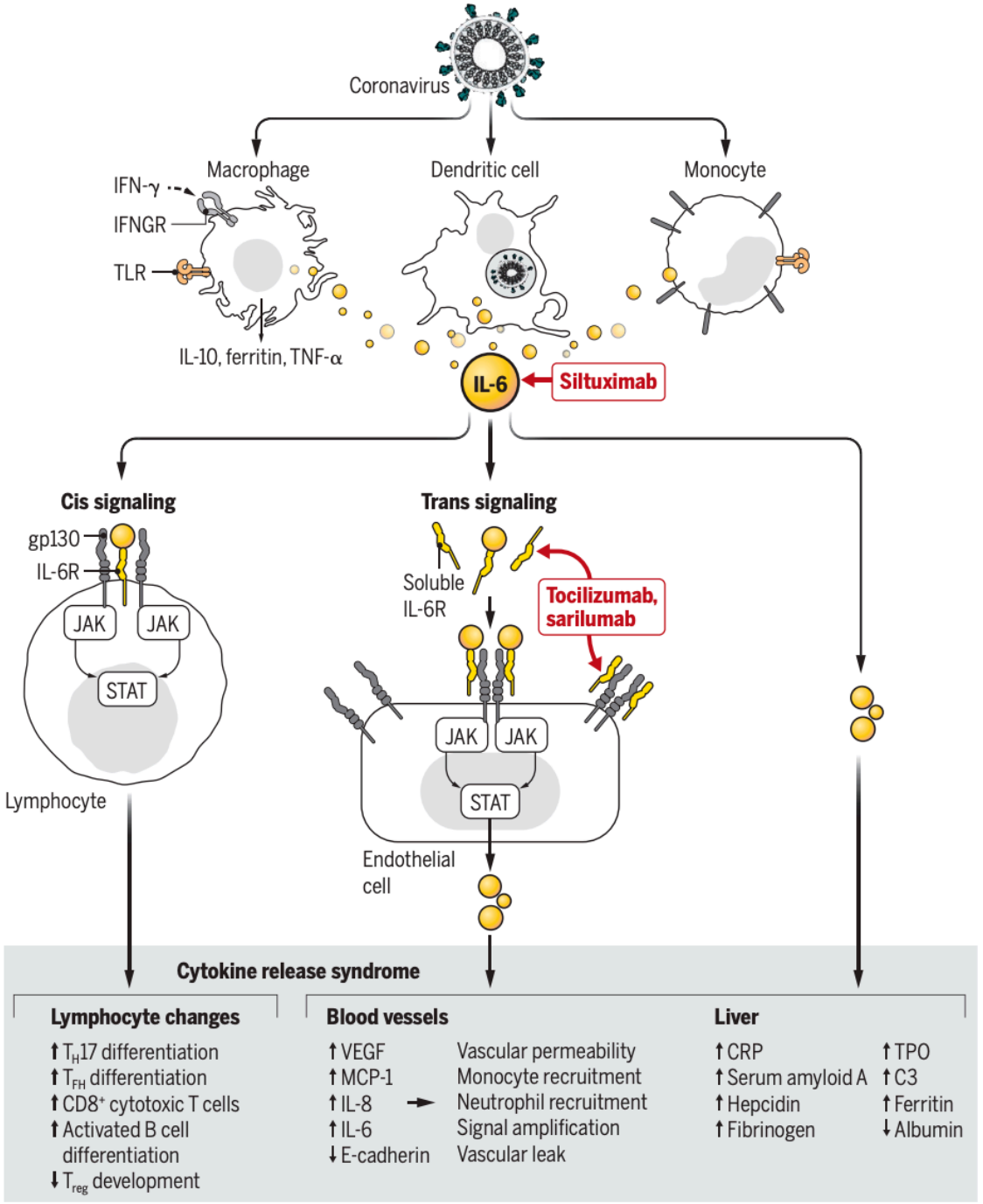


Images: CarBibles.com, Frontiers News (Apr 14, 2020)

# Hyperinflammation in COVID-19 – should we intervene?




Images: CarBibles.com, Frontiers News (Apr 14, 2020), Pixabay, Wikimedia




## Tocilizumab

- Monoclonal antibody
- Binds IL-6 receptor
- FDA indications for RA and inflammatory arthritis, giant cell arteritis
- Approved for cytokine release syndrome after CAR-T cell therapy

June C, Science 2020

# Where are we going?

1. COVID-19 and ‘cytokine storm’
2. **Tocilizumab: what is the evidence?**
3. Lessons learned
   - Targeted immunomodulators
   - Weighing the evidence (or, guzzling from the COVID-19 firehose)

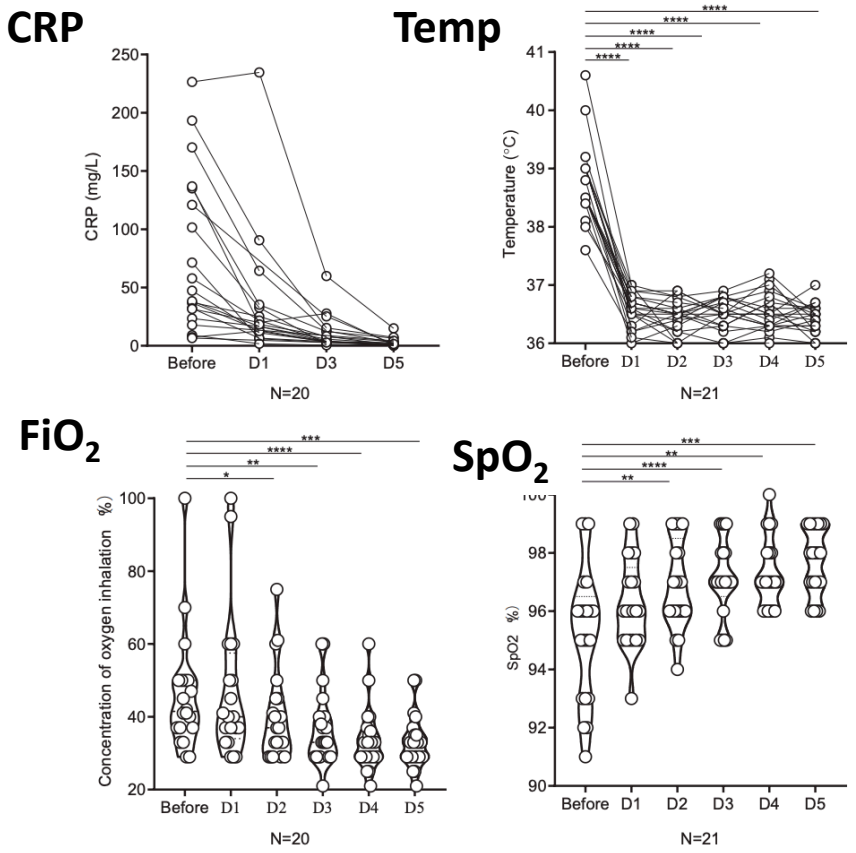
# Early non-randomized studies of IL-6 blockade

## Effective treatment of severe COVID-19 patients with tocilizumab

Xiaoling Xu[a,1,2], Mingfeng Han[b,1], Tiantian Li[a], Wei Sun[b], Dongsheng Wang[a], Binqing Fu[c,d], Yonggang Zhou[c,d], Xiaohu Zheng[c,d], Yun Yang[e], Xiuyong Li[f], Xiaohua Zhang[b], Aijun Pan[e], and Haiming Wei[c,d,2]

**China:** Two-center retrospective study

- 20 pts with severe or critical COVID-19
- Improved oxygenation, temp, markers




Xu X, PNAS 2020

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**China:** Two-center retrospective study

- 20 pts with severe or critical COVID-19
- Improved oxygenation, temp, markers

**Tocilizumab treatment in COVID-19: A single center experience**

Pan Luo | Yi Liu | Lin Qiu | Xiulan Liu | Dong Liu | Juan Li

**China:** Single-center retrospective study

- 15 patients with mod. to critical COVID-19
- Mixed results, but “appears to be effective”

**Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19**

S. Sciascia[1,2], F. Aprà[2], A. Baffa[1,2], S. Baldovino[1,2], D. Boaro[2], R. Boero[2], S. Bonora[2], A. Calcagno[2]

**Italy**: Multi-center, prospective open study

- 63 hospitalized pts with severe COVID-19
- Inflammatory markers, $PaO_2/FiO_2$ improved

Xu X, PNAS 2020; Luo P, J Med Virol 2020; Sciascia S, Clin Exp Rheum 2020

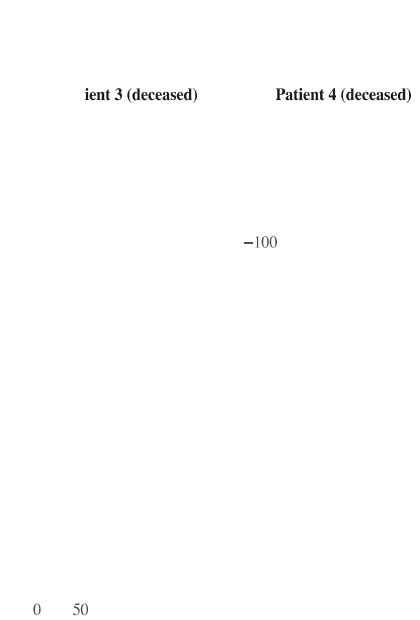
# What can we learn from our own patients?

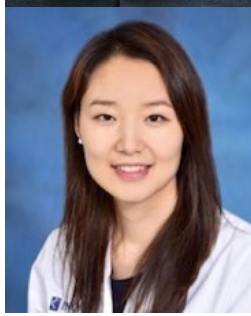
## CRP

- Early description of tocilizumab at UNC (n=11)
- CRP rapidly normalized, as previously reported
- **But no clear evidence of improvement** in oxygen requirements, temperature, and other markers

## $FiO_2$

## Temp



Rimland C, Morgan C et al. medRxiv 2020 (2020.05.13.20100404)

# Increasing off-label usage and positive observational studies

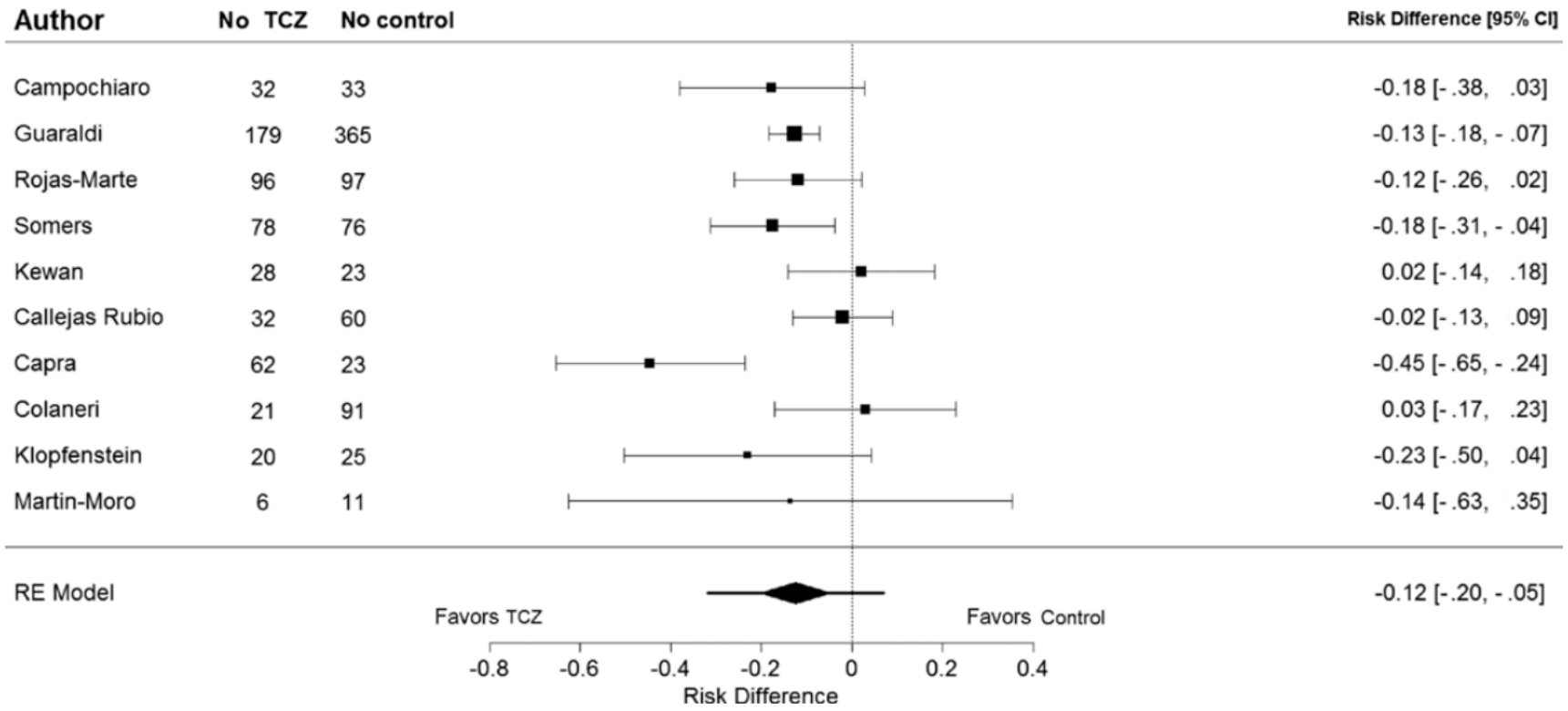
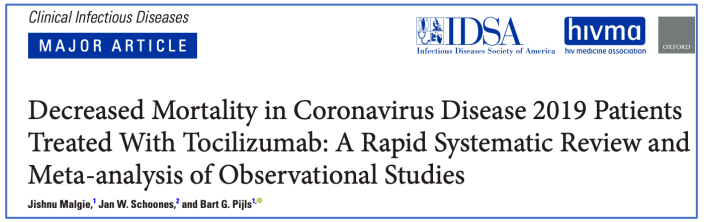


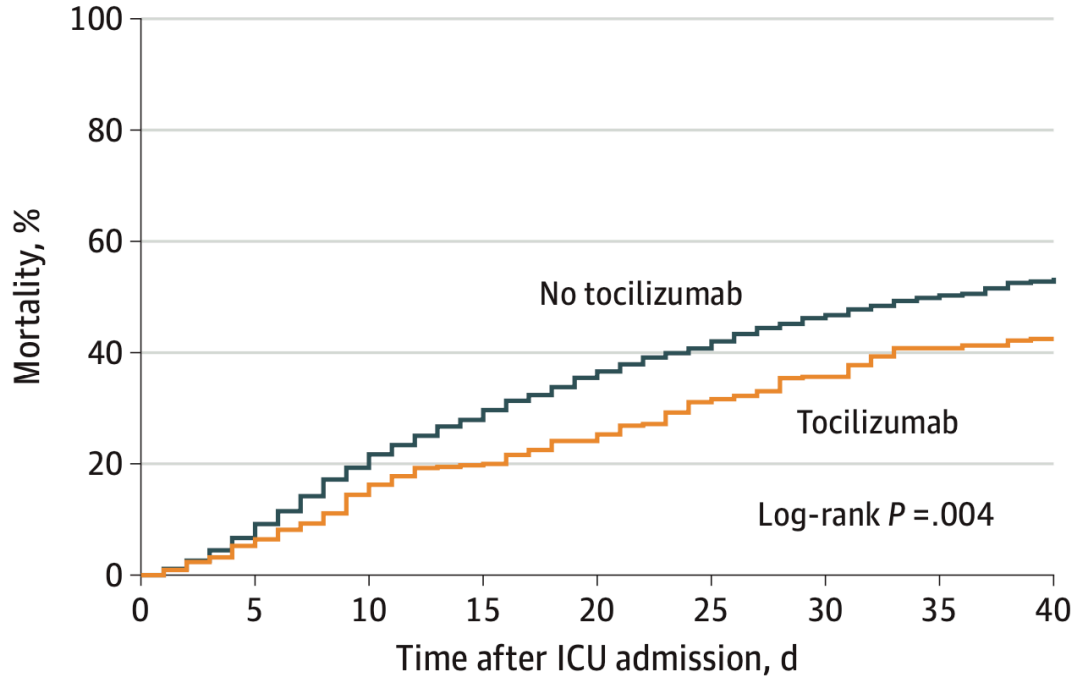

**Figure 2.** Forest plot showing the risk difference in mortality between patients treated with tocilizumab (TCZ) and patients not treated with TCZ. Meta-analysis on 10 observational studies comprising 1358 patients showed that mortality was 12% lower for patients with coronavirus disease 2019 (COVID-19) treated with TCZ compared to those not treated with TCZ. Abbreviations: CI, confidence interval; RE, Random Effects; TCZ, tocilizumab.




- Meta-analysis of 10 observational studies including controls
- 12% lower mortality in tocilizumab-treated patients

Malgie J, Clin Infect Dis 2020

# More evidence for efficacy from observational studies




No. at risk

| | | | | | |
|---|---|---|---|---|---|
| Tocilizumab | 419 | 311 | 190 | 110 | 50 |
| No tocilizumab | 3492 | 2460 | 1433 | 789 | 369 |

JAMA Internal Medicine | Original Investigation

**Association Between Early Treatment With Tocilizumab and Mortality Among Critically Ill Patients With COVID-19**

Shruti Gupta, MD, MPH; Wei Wang, PhD; Salim S. Hayek, MD; Lili Chan, MD, MSCR; Kusum S. Mathews, MD, MPH, MSCR; Michal L. Melamed, MD, MHS; Samantha K. Brenner, MD, MPH; Amanda Leonberg-Yoo, MD, MS; Edward J. Schenck, MD, MS; Jared Radbel, MD; Jochen Reiser, MD, PhD;

- From the STOP-COVID registry
- **Observational study** at 68 sites across the US
- 4,485 critically ill patients in ICUs
- **Thresholds for efficacy met:**
  - ✓ Time to death: HR 0.71 [0.56, 0.92]
  - ✓ 30-day mortality: RD 9.6% [3.1, 16.0]
- **Improved 30d mortality:**
  - ✓ 27.5% vs. 37.1%, RD 9.6% [3.1, 16.0]

Gupta S, JAMA Int Med 2020

# But RCTs were largely negative…

JAMA Internal Medicine | Original Investigation

## Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia

A Randomized Clinical Trial

Carlo Salvarani, MD; Giovanni Dolci, MD; Marco Massari, MD; Domenico Franco Merlo, PhD; Silvio Cavuto, BSc; Luisa Savoldi, BSc; P
Fabrizio Boni, MD; Luca Braglia, BSc; Caterina Turrà, MSc; Pier Ferruccio Ballerini, MD; Roberto Sciascia, MD; Lorenzo Zammarchi, M

JAMA Internal Medicine | Original Investigation

## Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia

A Randomized Clinical Trial

Olivier Hermine, MD, PhD; Xavier Mariette, MD, PhD; Pierre-Louis Tharaux, MD, PhD; Matthieu Resche-Rigon, MD, PhD; Raphaël Porcher, PhD; Philippe Ravaud, MD, PhD; for the CORIMUNO-19 Collaborative Group

*Roche provides an update on the phase III COVACTA trial of Actemra/RoActemra in hospitalised patients with severe COVID-19 associated pneumonia*

- **COVACTA trial did not meet its primary endpoint of improved clinical status in patients with COVID-19 associated pneumonia, or the key secondary endpoint of reduced pa**

*Roche's phase III EMPACTA study showed Actemra/RoActemra reduced the likelihood of needing mechanical ventilation in hospitalised patients with COVID-19 associated pneumonia*

- **EMPACTA is the first global phase III trial to show efficacy with Actemra/RoActemra in COVID-19 associated pneumonia and the first with a focus on enrolling largely underserved and minority patients**
- **There was no statistical difference in mortality between patients who received Actemra/RoActemra or placebo**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Efficacy of Tocilizumab in Patients Hospitalized with Covid-19

J.H. Stone, M.J. Frigault, N.J. Serling-Boyd, A.D. Fernandes, L. Harvey, A.S. Foulkes, N.K. Horick, B.C. Healy, R. Shah, A.M. Bensaci, A.E. Woolley

Salvarini JAMA Int Med 2020; CORIMMUNO JAMA Int Med 2020; Stone J NEJM 2020; F. Hoffman-La Roche Ltd (press releases)

# Italy (RCT-TCZ-COVID-19) - stopped for futility

JAMA Internal Medicine | Original Investigation

**Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia**
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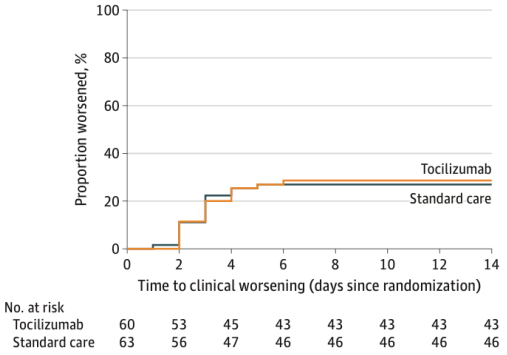
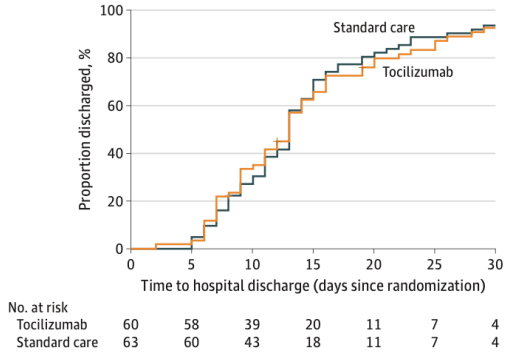
- 24 sites in Italy, 126 subjects with severe COVID-19
- On oxygen (low- or high-flow)
- Stopped early by DSMB for futility

**Cumulative clinical worsening**




**Hospital discharge rates**




- **Thresholds for efficacy not met**: ✗ PaO2/FiO2 <150mmHg, ICU admission, or death: RR 1.05 [0.59, 1.86]**
- **No 28d mortality benefit**: ✗ 3.3% vs. 1.6%, RR 2.10 [0.20, 22.6]

Salvarini S, JAMA Int Med 2020

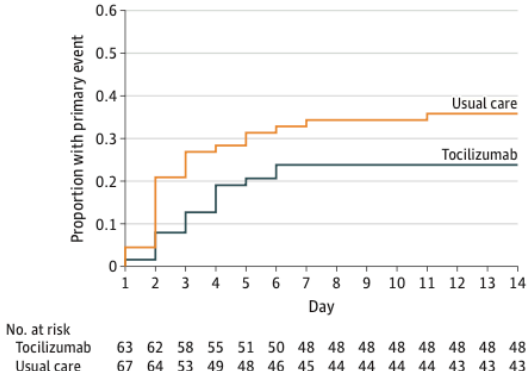
# France (CORIMUNO-TOCI-1) - barely meets one efficacy threshold

JAMA Internal Medicine | Original Investigation

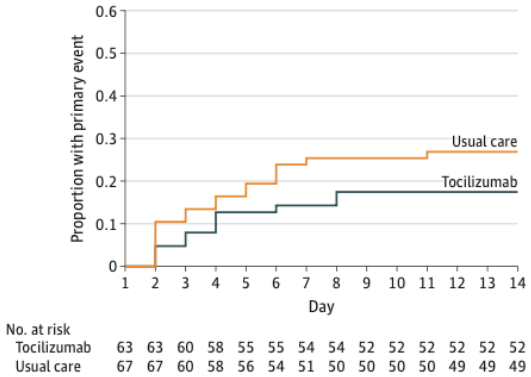
**Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia**
A Randomized Clinical Trial

Olivier Hermine, MD, PhD; Xavier Mariette, MD, PhD; Pierre-Louis Tharaux, MD, PhD; Matthieu Resche-Rigon, MD, PhD; Raphaël Porcher, PhD; Philippe Ravaud, MD, PhD; for the CORIMUNO-19 Collaborative Group

**Death or MV, high-flow, NIV at d14**




**Death or MV at d14**




- 9 sites in France, 131 subjects with severe COVID-19
- On oxygen (but no high-flow, mech vent, or ECMO)
- **1/2 thresholds for efficacy met**:
  - ✘ WHO-CPS score >5 on d4: ARD -9.0% (90% CrI -21.0 to +3.1), posterior prob. of ARD<0 of 89.0%
  - ✓ Survival without NIV or MV by d14: HR 0.58 (90%CrI 0.33 to 1.00), posterior prob. of HR<1 of 95.0%
- **No 28d mortality benefit**:
  - ✘ 11.1% vs. 11.9%, aHR 0.92 [0.33, 2.53]

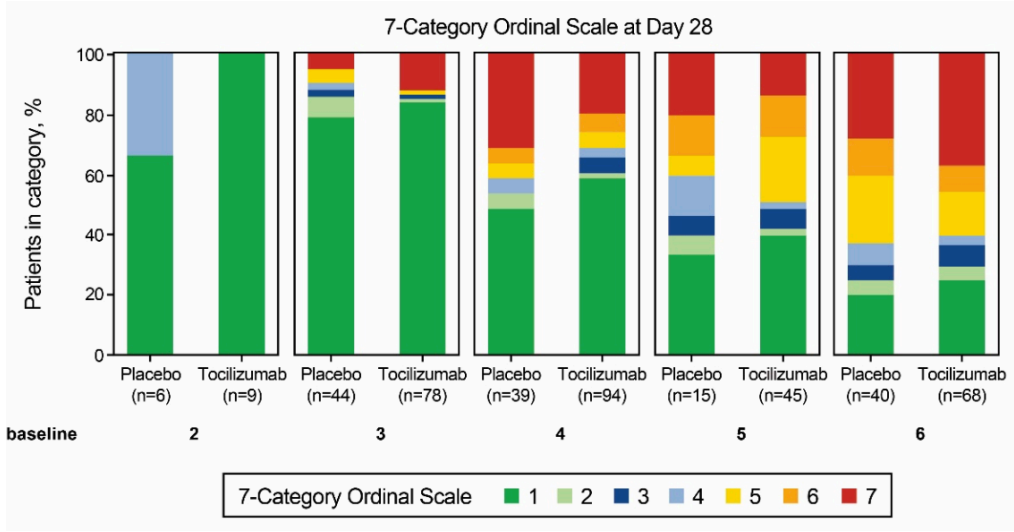
Hermine O, JAMA Int Med 2020

# N. America and Europe (COVACTA) - negative

*Roche provides an update on the phase III COVACTA trial of Actemra/RoActemra in hospitalised patients with severe COVID-19 associated pneumonia*

- **COVACTA trial did not meet its primary endpoint of improved clinical status in patients with COVID-19 associated pneumonia, or the key secondary endpoint of reduced patient mortality**

**Peer-reviewed analysis pending**




- 67 sites in Canada, Denmark, France, Germany, Italy, the Netherlands, Spain, UK, and the US
- 450 subjects with severe and critical COVID-19
- Double-blind, placebo-controlled
- **Conducted by Roche** (tocilizumab's manufacturer)

- **Thresholds for efficacy not met**: ✗ Difference in clinical status using a 7-category scale at d28: OR 1.19 [0.81, 1.76]

- **No 28d mortality benefit**: ✗ 19.7% vs. 19.4%, ARD 0.3% [-7.6, 8.2]

Derived from clinicaltrials.gov; Roche press release (roche.com/investors/updates/inv-update-2020-07-29.htm); Rosas IO, medRxiv 2020

# Americas and Africa (EMPACTA) – meets efficacy threshold

*Roche's phase III EMPACTA study showed Actemra/RoActemra reduced the likelihood of needing mechanical ventilation in hospitalised patients with COVID-19 associated pneumonia*

- **EMPACTA is the first global phase III trial to show efficacy with Actemra/RoActemra in COVID-19 associated pneumonia and the first with a focus on enrolling largely underserved and minority patients**
- **There was no statistical difference in mortality between patients who received Actemra/RoActemra or placebo**

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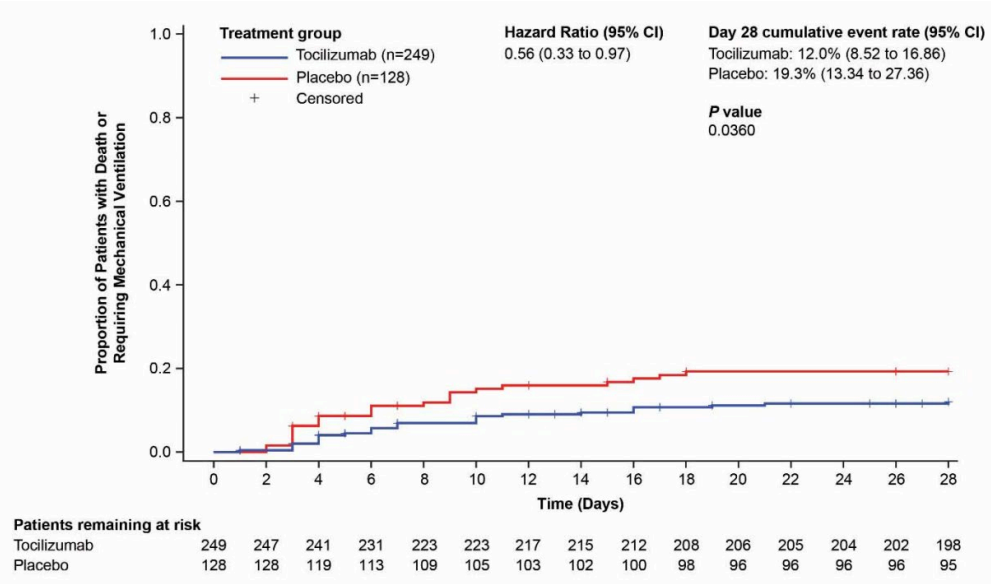



- 69 sites in Brazil, Kenya, Mexico, Peru, South Africa, & US
- 389 subjects with severe COVID-19, 2:1 to TCZ:placebo
- Focus on 'minority' racial/ethnic groups
- Majority received steroids (~80%) and remdesivir (~55%)
- Double-blind, placebo-controlled
- **Conducted by Roche** (tocilizumab's manufacturer)

- **Thresholds for efficacy met**: ✓ Death or MV by day 28: HR 0.56 [0.32, 0.97]

- **No 28d mortality benefit**: ✗ 10.4% vs. 8.6%, ARD 2.0% [-5.2, 7.8]

Clinicaltrials.gov; Roche press release (roche.com/media/releases/med-cor-2020-09-18.htm); Salama C medRxiv 2020

# Trying to make sense of it all…

**Table. Comparison of Major Tocilizumab COVID-19 Studies Reported to Date**

| Study characteristic | Gupta et al[3] (STOP-COVID) | Salvarani et al[1] (RCT-TCZ-COVID-19) | Hermine et al[2] (CORIMUNO-TOCI-1) | COVACTA[12] | EMPACTA[13] |
|---|---|---|---|---|---|
| Design | | | | | |
| Type | Observational retrospective | Randomized prospective | Randomized prospective | Randomized prospective | Randomized prospective |
| Blinded | NA | No | No | Yes (double) | Yes (double) |
| Placebo-controlled | NA | No | No | Yes | Yes |
| Enrollment | | | | | |
| No. of sites | 68 | 24 | 9 | 67 | 69 |
| Countries | US | Italy | France | Canada, Denmark, France, Germany, Italy, the Netherlands, Spain, United Kingdom, US | Brazil, Kenya, Mexico, Peru, South Africa, US |
| No. of participants | 3924 | 126 | 131 | 450 | 389 |
| No. tocilizumab treated | 433 | 60[a] | 63 | 225[b] | 194[b] |
| Clinical severity[c] | | | | | |
| Moderate | No | No | No | No | No |
| Severe | Yes | Yes | Yes | Yes | Yes |
| Critical | Yes | No | No | Yes | No |
| Intervention | | | | | |
| Tocilizumab | Within 2 d of ICU admission | 8 mg/kg ×2 Doses, 12 h apart | 8 mg/kg ×1, Possible second dose on day 3 | 8 mg/kg ×1, Possible second dose | 8 mg/kg ×1, Possible second dose |
| Comparator | Usual care | Usual care | Usual care | Usual care plus placebo | Usual care plus placebo |
| Outcomes[d] | | | | | |
| Primary, effect size | Time to death: Threshold for efficacy met; HR, 0.71 (95% CI, 0.56 to 0.92)<br>30-d mortality: Threshold for efficacy met; RD, 9.6% (95% CI, 3.1% to 16.0%) | $Pao_2$:$Fio_2$ <150 mm Hg, ICU admission, or death: Threshold for efficacy not met; RR, 1.05 (95% CI, 0.59 to 1.86)[e] | WHO-CPS score >5 on day 4: Threshold for efficacy not met; ARD, −9.0% (90% CrI, −21.0% to 3.1%); posterior probability of ARD <0 of 89.0%<br>Survival without NIV or MV by day 14: Threshold for efficacy met; HR, 0.58 (90% CrI, 0.33 to 1.00), posterior probability of HR<1 of 95.0% | Difference in clinical status using a 7-category scale at day 28: Threshold for efficacy not met; OR, 1.19 (95% CI, 0.81 to 1.76) | Death or MV by day 28: Threshold for efficacy met; HR, 0.56 (95% CI, 0.32 to 0.97) |
| 28- or 30-d mortality, tocilizumab vs comparator, effect size[f] | 27.5% vs 37.1%; RD, 9.6% (95% CI, 3.1% to 16.0%) | 3.3% vs 1.6%; RR, 2.10 (95% CI, 0.20 to 22.6) | 11.1% vs 11.9%; aHR, 0.92 (95% CI, 0.33 to 2.53) | 19.7% vs 19.4%; ARD, 0.3% (95% CI, −7.6% to 8.2%) | 10.4% vs 8.6%; ARD, 2.0% (95% CI, −5.2% to 7.8%) |
| Trial registration | NCT04343898 | NCT04346355 | NCT04331808 | NCT04320615 | NCT04372186 |

Time to Reassess Tocilizumab's Role in COVID-19 Pneumonia

Jonathan B. Parr, MD, MPH

Parr JB JAMA Int Med 2020

# RCTs do not support routine tocilizumab use

Table. Comparison of Major Tocilizumab COVID-19 Studies Reported to Date

| Study characteristic | Gupta et al[3] (STOP-COVID) | Salvarani et al[1] (RCT-TCZ-COVID-19) | Hermine et al[2] (CORIMUNO-TOCI-1) | COVACTA[12] | EMPACTA[13] |
|---|---|---|---|---|---|
| Design | | | | | |
| Type | Observational retrospective | Randomized prospective | Ra | | |
| Blinded | NA | No | No | | |
| Placebo-controlled | NA | No | No | | |
| Enroll | | | | | |
| No. of sites | 68 | 24 | 9 | | |
| Countries | US | Italy | Fr | | |
| No. of participants | 3924 | 126 | 13 | | |
| No. tocilizumab treated | 433 | 60[a] | 63 | | |
| Clinical severity[c] | | | | | |
| Moderate | No | No | No | | |
| Severe | Yes | Yes | Ye | | |
| Critical | Yes | No | No | | |
| Intervention | | | | | |
| Tocilizumab | Within 2 d of ICU admission | 8 mg/kg ×2 Doses, 12 h apart | 8 p se | | |
| Co | Usual care | Usual care | Us | | |
| Outc | | | | | |
| Primary, effect size | Time to death: Threshold for efficacy met; HR, 0.71 (95% CI, 0.56 to 0.92)<br>30-d mortality: Threshold for efficacy met; RD, 9.6% (95% CI, 3.1% to 16.0%) | $Pao_2$:$Fio_2$ <150 mm Hg, ICU admission, or death: Threshold for efficacy not met; RR, 1.05 (95% CI, 0.59 to 1.86)[e] | WI 4: no Cr po AR<br>Survival without NIV or MV by day 14: Threshold for efficacy met; HR, 0.58 (90% CrI, 0.33 to 1.00), posterior probability of HR<1 of 95.0% | | |
| 28- or 30-d mortality, tocilizumab vs | 27.5% vs 37.1%; RD, 9.6% (95% CI, 3.1% to 16.0%) | 3.3% vs 1.6%; RR, 2.10 (95% CI, 0.20 to 22.6) | 11.1% vs 11.9%; aHR, 0.92 (95% CI, 0.33 to 2.53) | 19.7% vs 19.4%; ARD, 0.3% (95% CI, −7.6% to 8.2%) | 10.4% vs 8.6%; ARD, 2.0% (95% CI, −5.2% to 7.8%) |

T

## Primary outcomes

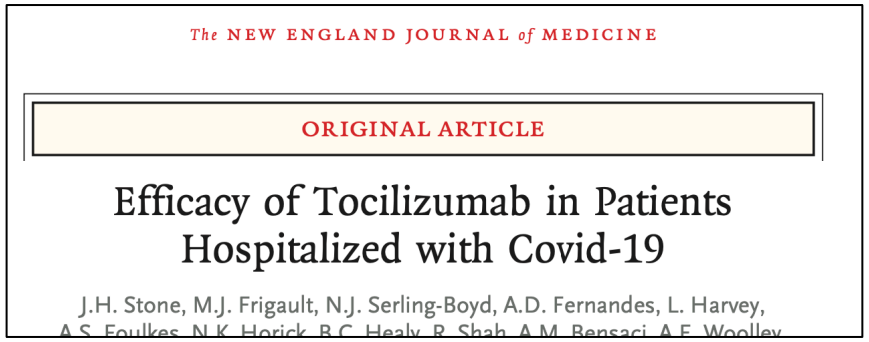
## 28d overall mortality

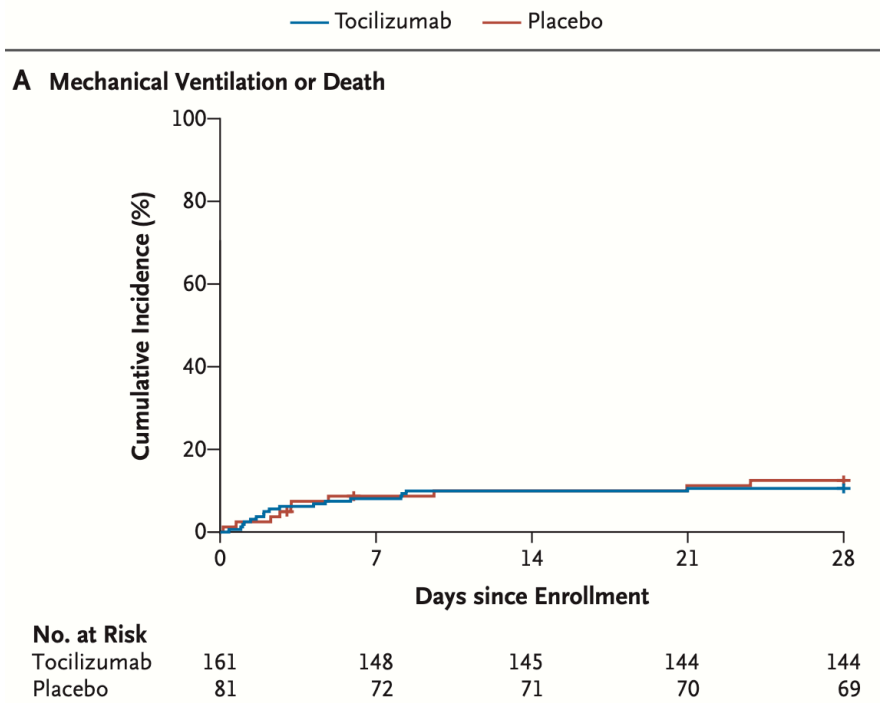
## Randomized trial results

| | | | |
|---|---|---|---|
| $Pao_2$:$Fio_2$ <150 mm Hg, ICU admission, or death: Threshold for efficacy not met; RR, 1.05 (95% CI, 0.59 to 1.86)[e] | WHO-CPS score >5 on day 4: Threshold for efficacy not met; ARD, −9.0% (90% CrI, −21.0% to 3.1%); posterior probability of ARD <0 of 89.0%<br>Survival without NIV or MV by day 14: Threshold for efficacy met; HR, 0.58 (90% CrI, 0.33 to 1.00), posterior probability of HR<1 of 95.0% | Difference in clinical status using a 7-category scale at day 28: Threshold for efficacy not met; OR, 1.19 (95% CI, 0.81 to 1.76) | Death or MV by day 28: Threshold for efficacy met; HR, 0.56 (95% CI, 0.32 to 0.97) |
| 3.3% vs 1.6%; RR, 2.10 (95% CI, 0.20 to 22.6) | 11.1% vs 11.9%; aHR, 0.92 (95% CI, 0.33 to 2.53) | 19.7% vs 19.4%; ARD, 0.3% (95% CI, −7.6% to 8.2%) | 10.4% vs 8.6%; ARD, 2.0% (95% CI, −5.2% to 7.8%) |

Parr JB JAMA Int Med 2020

# Boston, USA (BACC Bay Tocilizumab) – negative




- 7 Boston-area hospitals
- 243 subjects with severe COVID-19, 2:1 to TCZ:placebo
- Double-blind, placebo-controlled
- Sponsored by Roche/Genentech (toci's manufacturer)

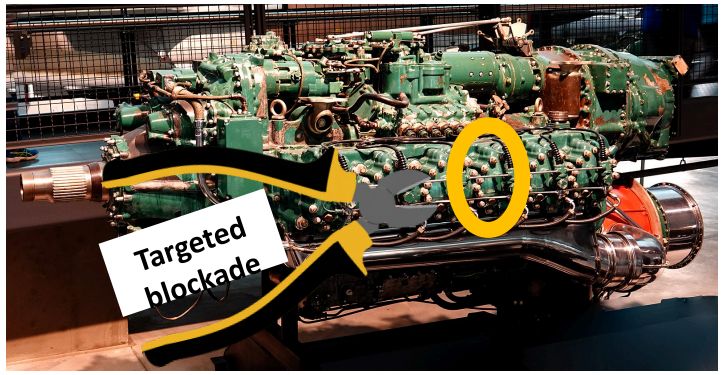
- **Thresholds for efficacy not met**:
  - ✘ Time to intubation or death: HR 0.83 [0.38, 1.8]
- **No 28d mortality benefit**:
  - ✘ 5.6% vs. 3.8%, HR 1.52 [0.41, 5.61]

Stone JH, NEJM 2020

# Where are we going?

1. COVID-19 and ‘cytokine storm’
2. Tocilizumab: what is the evidence?
3. **Lessons learned**
   - Targeted immunomodulators
   - Weighing the evidence (or, guzzling from the COVID-19 firehose)

# Immune-based therapies - which and when?


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19
A Meta-analysis

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group

**Clearly a role for immune-based therapies**

- Dexamethasone is now standard of care worldwide for those with COVID-19 who require oxygen

**Anakinra for severe forms of COVID-19: a cohort study**

Thomas Huet, Hélène Beaussier, Olivier Voisin, Stéphane Jouveshomme, Gaëlle Dauriat, Isabelle Lazareth, Emmanuelle Sacco,

**Early IL-1 receptor blockade in severe inflammatory respiratory failure complicating COVID-19**

Raphaël Cauchois[a,1]

**Suspension des inclusions en France dans les essais clinique évaluant l'anakinra dans la prise en charge de la COVID-19 - Point d'information**

29/10/2020

SANOFI

Press Release

Source: Sanofi (EURONEXT: SAN) (NASDAQ: SNY)

**Sanofi provides update on Kevzara® (sarilumab) Phase 3 trial in severe and critically ill COVID-19 patients outside the U.S.**

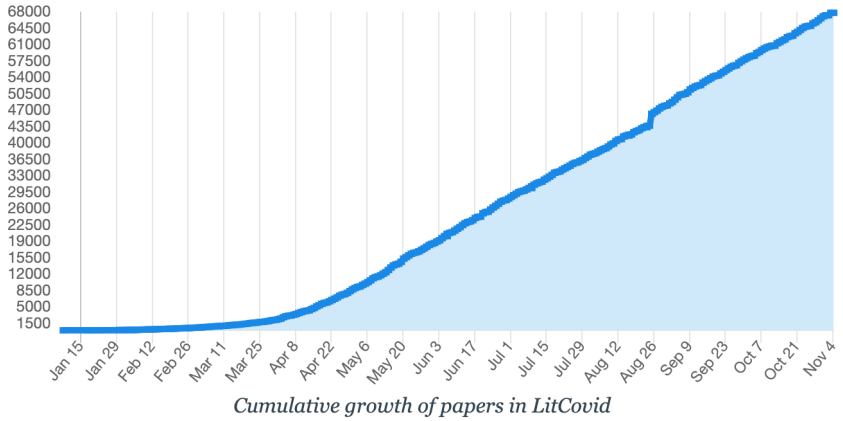
**Role of targeted cytokine/chemokine blockade remains unclear**

- Increasing positive results from anakinra (anti-IL1R) observational studies, but RCT stopped in France due to excess mortality in treatment group.
- Sarilumab (anti-IL6R) RCT failed.
- Siltuximab (anti-IL6), canakinumab (anti-IL1B), vilobelimab (anti-C5a), many many others – results pending…

RECOVERY investigators, NEJM 2020; WHO REACT, JAMA 2020; Huet T Lancet 2020; Cauchois R PNAS 2020; ANSM press release 10/29/20; Sanofi press release 9/1/20; | Images: CarBibles.com, Pixabay, Wikimedia

# Now is the time to rely upon randomized trials

- >67,000 COVID-19 publications to-date
- >2,500 clinical trials registered



*Cumulative growth of papers in LitCovid*

## Summary Recommendations

### Dexamethasone and Other Corticosteroids

- The COVID-19 Treatment Guidelines Panel's (the Panel's)recommendations on the use of dexamethasone (or other corticosteroids) with or without remdesivir can be found in the Therapeutic Management of Patients with COVID-19.

### Other Immunomodulators

There are insufficient data for the Panel to recommend either for or against the use of the following immunomodulators for the treatment of COVID-19:

- Interleukin (IL)-1 inhibitors (e.g., **anakinra**).
- **Interferon beta** for the treatment of early (i.e., <7 days from symptom onset) mild and moderate COVID-19.

The Panel **recommends against** the use of the following immunomodulators for the treatment of COVID-19, except in a clinical trial:

- Anti-IL-6 receptor monoclonal antibodies (e.g., **sarilumab**, **tocilizumab**) or anti-IL-6 monoclonal antibody (**siltuximab**) **(BI)**.
- **Interferons (alfa or beta)** for the treatment of severely or critically ill patients with COVID-19 **(AIII)**.
- Bruton's tyrosine kinase inhibitors (e.g., **acalabrutinib**, **ibrutinib**, **zanubrutinib**) and Janus kinase inhibitors (e.g., **baricitinib**, **ruxolitinib**, **tofacitinib**) **(AIII)**.

LitCovid (ncbi.nlm.nih.gov/research/coronavirus/faq); ClinicalTrials.gov; NIH (covid19treatmentguidelines.nih.gov)

# Summary

- A hyperinflammatory state can be seen in COVID-19.
- Observational studies supported rapid uptake of targeted immune-based therapies like tocilizumab, but…
- Randomized trials to-date do not support routine tocilizumab use. Additional RCT results are expected.
- **Data from high quality randomized controlled trials is essential** to identify therapeutics with real impact.

# Thank you!

ideelresearch.org

@jonbparr