New Immunomodulatory drugs in management of COVID-19

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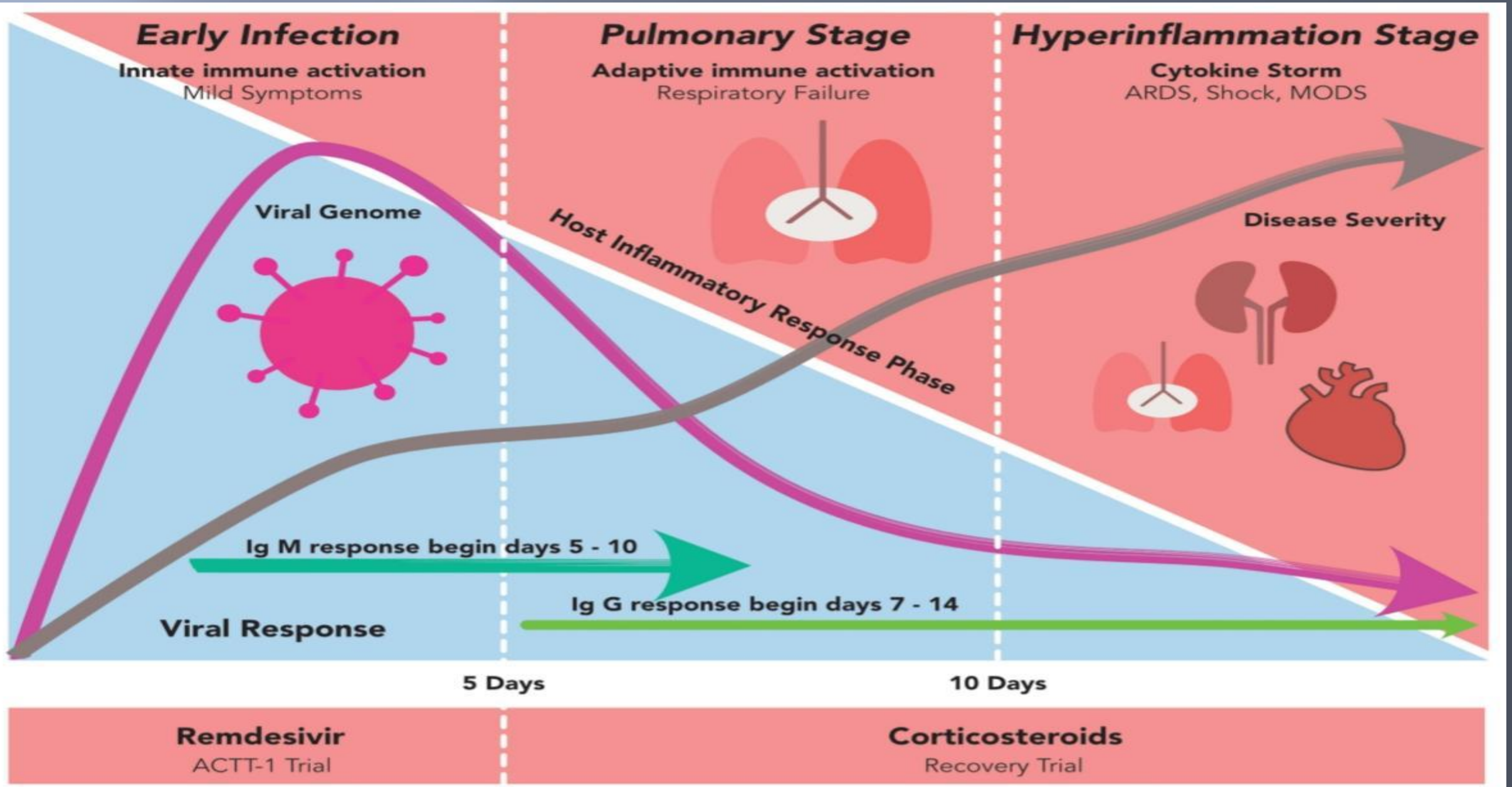
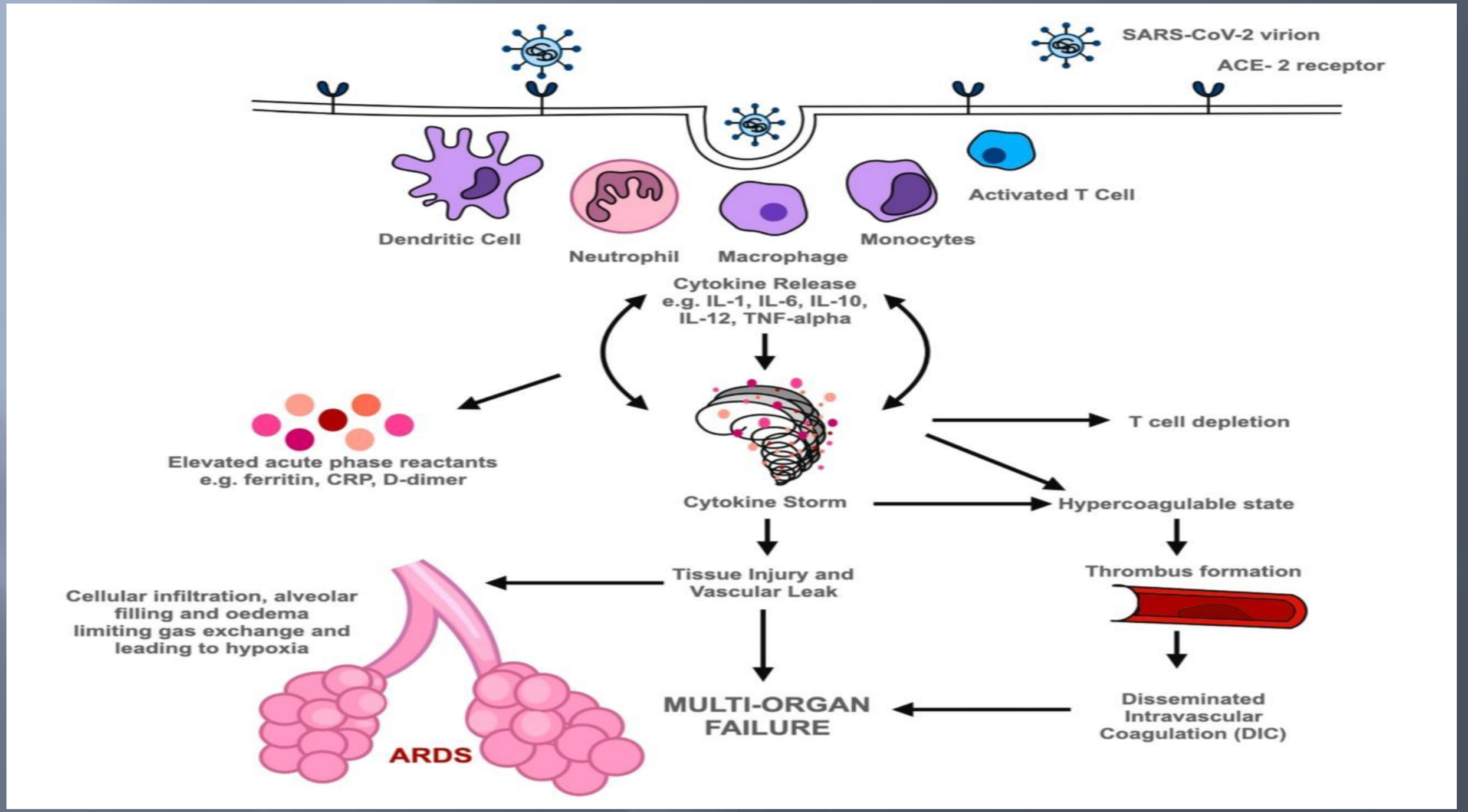

Early Infection
Innate immune activation
Mild Symptoms
Pulmonary Stage
Adaptive immune activation
Respiratory Failure
Hyperinflammation Stage
Cytokine Storm
ARDS, Shock, MODS
Viral Genome
Host Inflammatory Response Phase
Disease Severity
Ig M response begin days 5 - 10
Ig G response begin days 7 - 14
Viral Response
5 Days
10 Days
Remdesivir
ACTT-1 Trial
Corticosteroids
Recovery Trial


SARS-CoV-2 virion
ACE- 2 receptor
Activated T Cell
Dendritic Cell
Neutrophil
Macrophage
Monocytes
Cytokine Release
e.g. IL-1, IL-6, IL-10,
IL-12, TNF-alpha
Elevated acute phase reactants
e.g. ferritin, CRP, D-dimer
T cell depletion
Cytokine Storm
Hypercoagulable state
Thrombus formation
Tissue Injury and
Vascular Leak
Cellular infiltration, alveolar
filling and oedema
limiting gas exchange and
leading to hypoxia
ARDS
MULTI-ORGAN
FAILURE
Disseminated
Intravascular
Coagulation (DIC)

Dovepress

Immunomodulation as a Potent COVID-19 Pharmacotherapy:

Past:
Present:

20 July 2021 Volume 2021

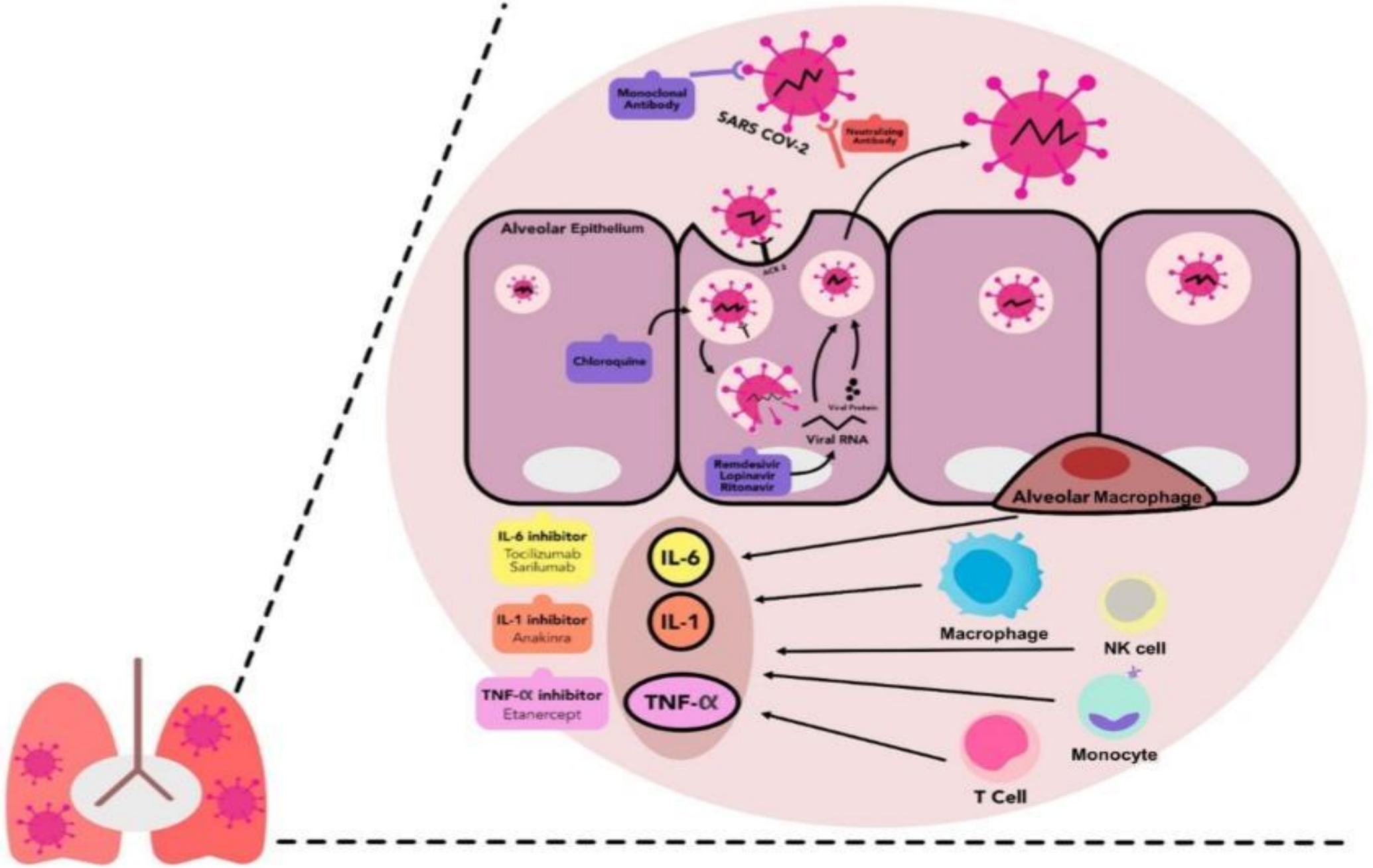
The hyperactive inflammatory response to SARS-CoV-2 infection plays a central role in the pathogenesis of COVID-19

recommendations on the use of the following immunomodulators for hospitalized patients according to their disease severity:

- ❑ *Corticosteroids:*
  Dexamethasone
- ❑ *Interleukin (IL-6) inhibitors:*
  Tocilizumab (or sarilumab)
- ❑ *Janus kinase (JAK) inhibitors:*
  Baricitinib (or tofacitinib)

insufficient evidence for the Panel to recommend either for or against the use

- ➢ *Anakinra*
- ➢ *Colchicine*
- ➢ *Fluvoxamine*
- ➢ *GM-CSF inhibitors*
- ➢ *Inhaled budesonide*
- ➢ *Interferon beta*


Monoclonal Antibody
SARS COV-2
Neutralizing Antibody
Alveolar Epithelium
ACE 2
Chloroquine
Viral Protein
Viral RNA
Remdesivir
Lopinavir
Ritonavir
Alveolar Macrophage
IL-6 inhibitor
Tocilizumab
Sarilumab
IL-1 inhibitor
Anakinra
TNF-α inhibitor
Etanercept
IL-6
IL-1
TNF-α
Macrophage
NK cell
Monocyte
T Cell

Interleukin-1 Inhibitors

- ***Anakinra** is a recombinant human IL-1 receptor antagonist .*
- ***Canakinumab** is a human monoclonal antibody that targets the beta subunit of IL-1*

There is insufficient evidence for the COVID-19 Treatment Guidelines Panel to recommend either for or against the use of anakinra for the treatment of COVID-19.

The Panel recommends against the use of canakinumab for the treatment of COVID-19, except in a clinical trial .

NIH | COVID-19 Treatment Guidelines

Articles

Effect of anakinra on mortality in patients with COVID-19: a systematic review and patient-level meta-analysis

The results of this systematic review and meta-analysis indicate that, in patients admitted to hospital with pneumonia due to COVID-19, treatment with anakinra reduces mortality when compared with standard of care, with or without placebo. This survival benefit was most profound in patients with hyperinflammation and CRP concentrations higher than 100 mg/L. We also observed a non-significant increase in the risk of adverse events with anakinra.

	Study type; individual patient data available?	Study setting and period	Inflammation criteria for inclusion	Number of patients		Route of administration	Steroid intake
				Anakinra group	Control group		
Cauchois et al (2020)[22]	Observational; yes	France: not mentioned	CRP >110 mg/L	12	10	Intravenous	No dexamethasone as standard of care; no other steroids
Huet et al (2020)[23]	Observational; yes	France: March, 2020 (historical controls); March 24–April 6, 2020 (anakinra group)	..	52	44	Subcutaneous	No dexamethasone as standard of care; steroid pulse in 2 of 52 patients in anakinra group
The CORIMUNO-19 Collaborative group (2021)[24]	Randomised controlled trial; no	France: April 8–26, 2020	CRP >25 mg/L	59	55	Intravenous	Dexamethasone in 1 of 59 in anakinra group; other glucocorticoids in 6 of 59 in anakinra group, and 8 of 55 in control group
Bozzi et al (2021)[25]	Observational; yes	Italy: Feb 25–March 30, 2020	CRP > 100 mg/L or ferritin >1000 µg/L, or both	65	55	Subcutaneous; intravenous if on invasive mechanical ventilation	No dexamethasone as standard of care; methylprednisolone co-administered with anakinra
Cavalli et al (2021)[26]	Observational; yes	Italy: March 10–17, 2020 (historical controls); March–May, 2020 (anakinra group)	CRP >100 mg/L or ferritin >900 µg/L	62	275	Intravenous	Dexamethasone in 54 of 275 controls and in 7 of 62 in anakinra group
Pontali et al (2021)[27]	Observational; no	Italy: Feb 26–April 29, 2020	CRP or ferritin >3 times the normal limits	63	44	Intravenous	No dexamethasone as standard of care; methylprednisolone in 33 of 63 patients in anakinra group
Kooistra et al (2020)[28]	Observational; yes	Netherlands: March 11–April 27, 2020	Ferritin >1800 µg/L; clinical hyperinflammation signs (persistent fever, unexplained progression of multiorgan failure)	21	39	Intravenous	Dexamethasone in 14 of 39 patients on standard of care and in 3 of 21 in anakinra group
Kyriazopoulou et al (2021)[29]	Observational; yes	Greece: April 16–Sept 12, 2020	suPAR >6 µg/L	130	130	Subcutaneous	Dexamethasone as standard of care in 47 of 130 controls and in 52 of 130 in anakinra group
Balkhair et al (2021)[30]	Observational; no	Oman: April 1–June 14, 2020 (historical controls); June 15–July 25, 2020 (anakinra group)	..	45	24	Subcutaneous	Dexamethasone in 24 of 45 in anakinra group, and 3 of 24 controls; methylprednisolone in 1 of 45 in anakinra group, and in 13 of 24 controls

CRP=C-reactive protein. suPAR=soluble urokinase-type plasminogen activator receptor.

Table 1: **Characteristics of included studies**

TNF Alpha Cytokine Inhibitors

Currently a wide variety of formulations of TNF inhibitors are used, including fully humanized biologics targeted to TNFα that include ***adalimumab, etanercept, and infliximab.***

The demonstration that TNFα is a key cytokine that is produced in a wide range of conditions causing inflammation, both in the acute and chronic phase

CellPress

Med

Review

The Potential for Repurposing Anti-TNF as a Therapy for the Treatment of COVID-19

Philip C. Robinson,[1,2,*] David F.L. Liew,[3,4] Jean W. Liew,[5] Claudia Monaco,[6] Duncan Richards,[6,7] Senthuran Shivakumar,[4] Helen L. Tanner,[1,2] and Marc Feldmann[6]

SUMMARY

Coronavirus disease 2019 (COVID-19) currently has few effective treatments. Given the uncertainty surrounding the effectiveness and uptake of a vaccine, it is important that the search for treatments continue. An exaggerated inflammatory state is likely responsible for much of the morbidity and mortality in COVID-19. Elevated levels of tumor necrosis factor (TNF), a key pro-inflammatory cytokine, have been shown to be associated with increased COVID-19 mortality. In patients with rheumatoid arthritis, TNF blockade reduces not only biologically active TNF but other pro-inflammatory cytokines important in COVID-19 hyperinflammation. Observational data from patients already on anti-TNF therapy show a reduced rate of COVID-19 poor outcomes and death compared with other immune-suppressing therapies. Anti-TNF has a long history of safe use, including in special at-risk populations, and is widely available. The case to adequately assess anti-TNF as a treatment for COVID-19 is compelling.

Med 1, 90–102, December 18, 2020

Infliximab as a COVID-19 treatment

CATALYST trial

Preprint: **Namilumab or infliximab compared to standard of care in hospitalised patients with COVID-19 (CATALYST): a phase 2 randomised adaptive trial** (Fisher et al.) – June 9, 2021 [11]

Summary

- Randomised, multi-arm, parallel group, open label, adaptive phase 2 proof-of-concept trial (CATALYST) of namilumab and infliximab, in order to determine prioritization for phase 3 trials
- Infliximab treatment: single IV dose of 5 mg/kg over 2 hours on day 1
- Namilumab treatment: single IV dose of 150mg given over 1 hour on day 1
- 35 patients received infliximab vs. 57 who received namilumab vs. 54 usual care
- Results: "The probabilities that namilumab and infliximab were superior to usual care in reducing CRP over time were 97% and 15% respectively. Consistent effects were seen in ward and ICU patients and aligned with clinical outcomes, such that the probability of discharge (WHO levels 1-3) at day 28 was 47% and 64% for ICU and ward patients on usual care, versus 66% and 77% for patients treated with namilumab. 134 adverse events occurred in 30/55 (54.5%) namilumab patients compared to 145 in 29/54 (53.7%) usual care patients. 102 events occurred in 20/29 (69.0%) infliximab patients versus 112 events in 17/34 (50.0%) usual care patients."

Conclusions

- **"Namilumab, but not infliximab, demonstrated proof-of-concept evidence for reduction in inflammation in hospitalised patients with COVID-19 pneumonia which was consistent with secondary clinical outcomes. Namilumab should be prioritised for further investigation in COVID-19."**

Table 2

Trials of TNF inhibitors in COVID-19.

Trial (Country)	Design	Intervention	Patient Cohort	Cases/Controls	Status	Trial Number
CATALYST (UK)	Randomised controlled platform study - prospective	Infliximab vs Nalimumab vs Mylotarg vs Standard	Hospitalized	60 patients per intervention arm 1:1	Completed Awaiting results	ISRCTN40580903
Tufts (USA)	Uncontrolled single arm study	Infliximab	Hospitalized	17 cases and 0 controls	Awaiting results	NCT04425538
ACTIV-1 (USA)	Randomised control platform study	Remdesivir + Infliximab vs Remdesivir + Abatacept vs Remdesivir +Cenicriviroc vs Standard	Hospitalized	2160 patients across 3 interventions and 1 control arm	Recruiting	NCT04593940
AVID-CC (UK)	Randomised controlled study	Adalimumab vs standard	Community	375 patients per arm 1:1	Recruiting	ISRCTN33260034
COMBAAT (USA)	Randomised controlled study	Adalimumab vs standard	Community	1444 patients across 2 arms 1:1	Pre-recruitment	NCT04705844
Xu (China)	Randomised controlled study	Adalimumab vs standard	Severe or critically ill	30 patients per arm 1:1	Suspended	ChiCTR2000030089

Dovepress

Immunomodulation as a Potent COVID-19 Pharmacotherapy: Future:

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Future Immunologic Targets for COVID-19

- retinoic acid inducible gene I-like receptor (RLR)
- NLRP3 inflammasome inhibitors
- complement inhibitors
- IL-18 inhibitors

Clinical Trial

muLTi-Arm Therapeutic study in pre-ICu patients admitted with Covid-19-Experimental drugs and mechanisms (TACTIC-E): A structured summary of a study protocol for a randomized controlled trial

Ing Ni Lu et al. Trials. 2020.

Complement system inhibition is also a potential therapeutic target for COVID-19. Preliminary data by Gao et al demonstrated the presence of complement hyperactivation (eg, widespread C3 and C5 complements deposition) in COVID19 and the activation, either through classical or alternative routes, can contribute to the maladaptive inflammatory response. Therefore, several clinical trials have been initiated to investigate the potential role of complement inhibitors in COVID-19.

For example, the combination of C5 inhibitor ravulizumab and JAK inhibitor baricitinib, which is now entering the Phase IV clinical trial.

Cellular & Molecular Immunology

www.nature.com/cmi

REVIEW ARTICLE OPEN

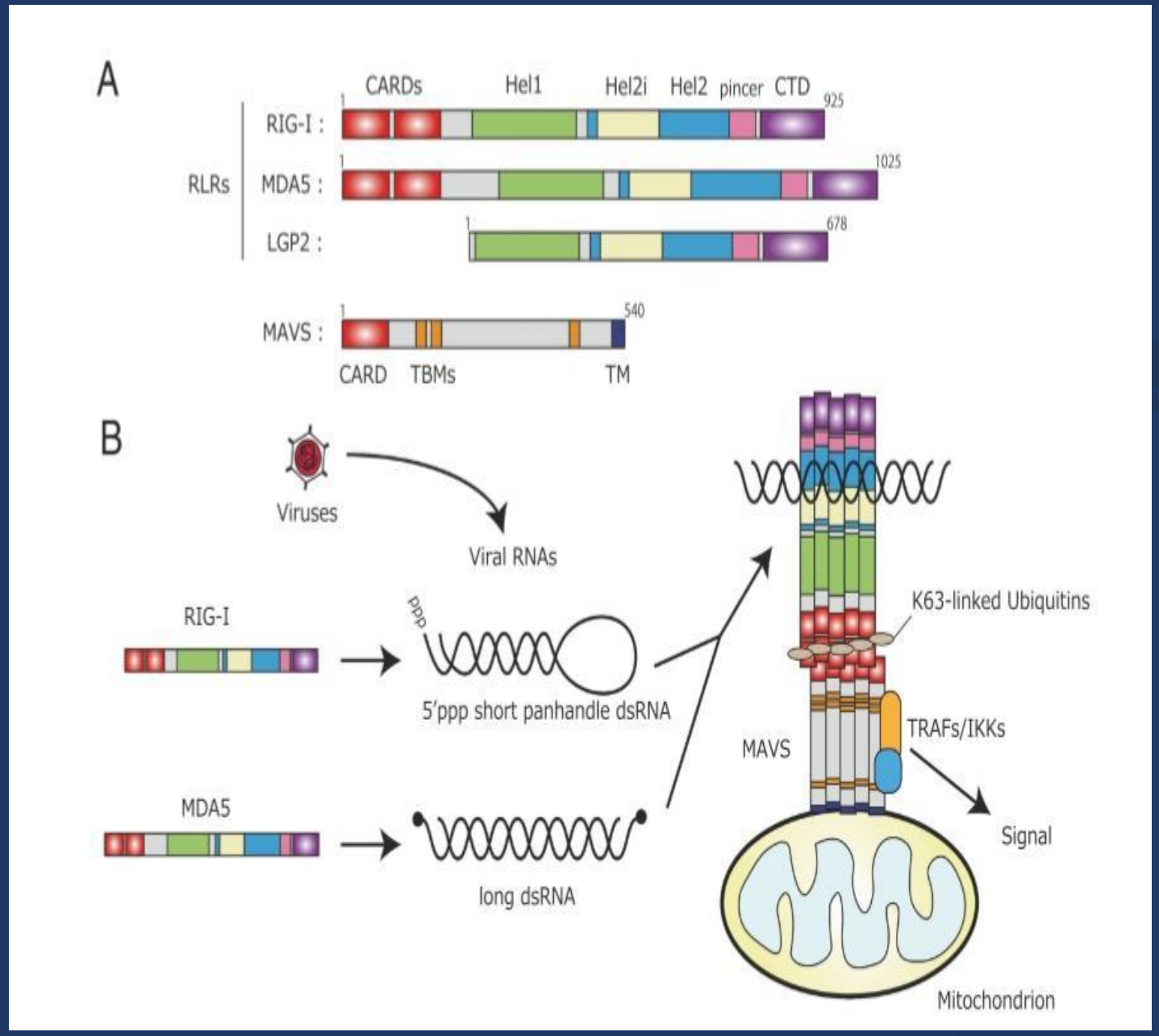
Regulation of RIG-I-like receptor-mediated signaling: interaction between host and viral factors

Koji Onomoto[1], Kazuhide Onoguchi[1] and Mitsutoshi Yoneyama[1]

Retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs) are RNA sensor molecules that play essential roles in innate antiviral immunity. Among the three RLRs encoded by the human genome, RIG-I and melanoma differentiation-associated gene 5, which contain N-terminal caspase recruitment domains, are activated upon the detection of viral RNAs in the cytoplasm of virus-infected cells. Activated RLRs induce downstream signaling via their interactions with mitochondrial antiviral signaling proteins and activate the production of type I and III interferons and inflammatory cytokines. Recent studies have shown that RLR-mediated signaling is regulated by interactions with endogenous RNAs and host proteins, such as those involved in stress responses and posttranslational modifications. Since RLR-mediated cytokine production is also involved in the regulation of acquired immunity, the deregulation of RLR-mediated signaling is associated with autoimmune and autoinflammatory disorders. Moreover, RLR-mediated signaling might be involved in the aberrant cytokine production observed in coronavirus disease 2019. Since the discovery of RLRs in 2004, significant progress has been made in understanding the mechanisms underlying the activation and regulation of RLR-mediated signaling pathways. Here, we review the recent advances in the understanding of regulated RNA recognition and signal activation by RLRs, focusing on the interactions between various host and viral factors.

Keywords: RIG-I-like receptors; Viral infection; Innate immunity; Stress response

Cellular & Molecular Immunology _####################_; https://doi.org/10.1038/s41423-020-00602-7



RLR is activated following the identification of viral RNAs in the cytoplasm of infected cells, initiating the production of type I and III IFNs and inflammatory cytokines. Therefore, the inhibition of RLR could alter the interactions between host and viral factors, which potentially prevent the activation of excessive inflammatory response in COVID-19.

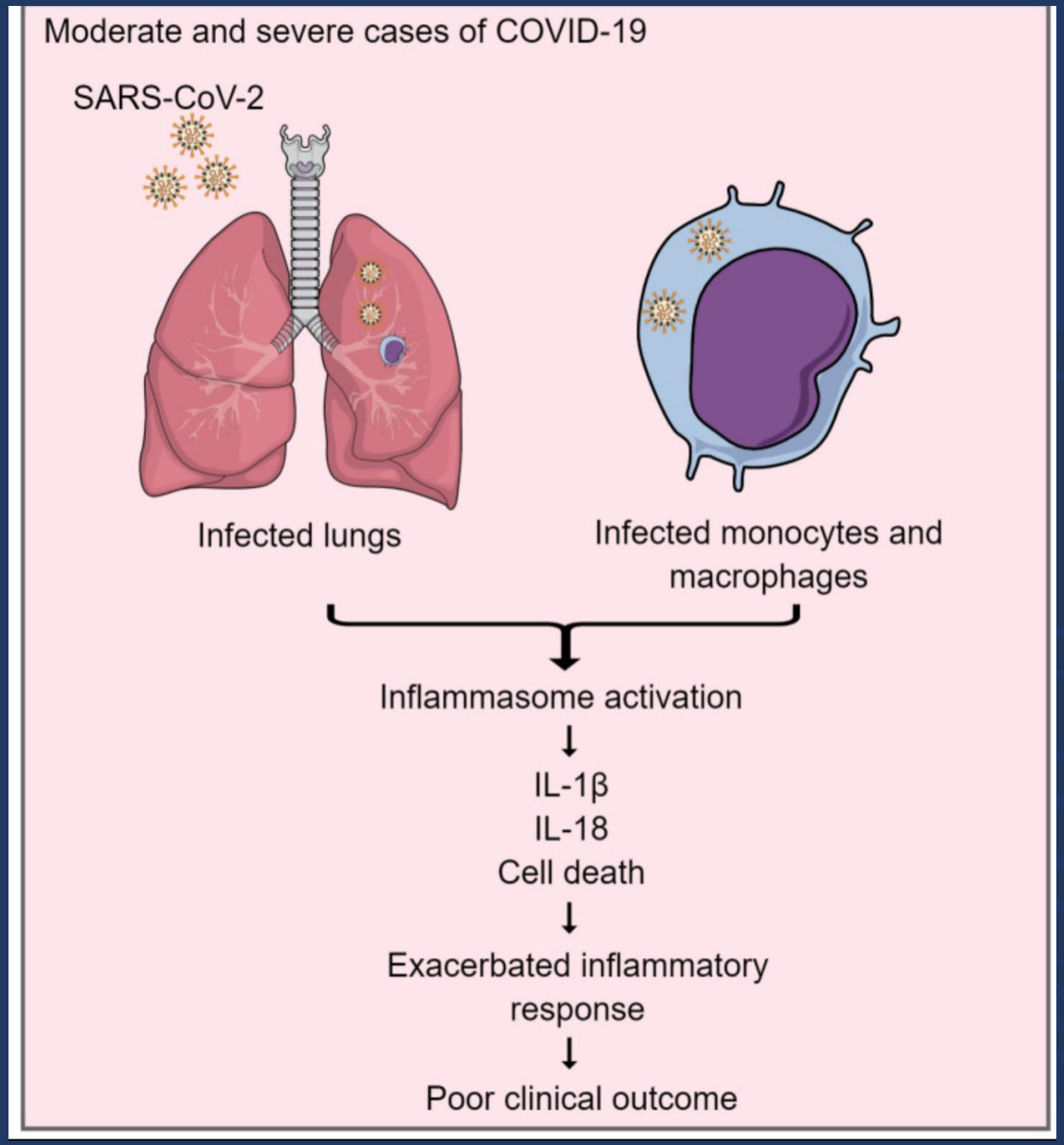
JEM Journal of Experimental Medicine

BRIEF DEFINITIVE REPORT

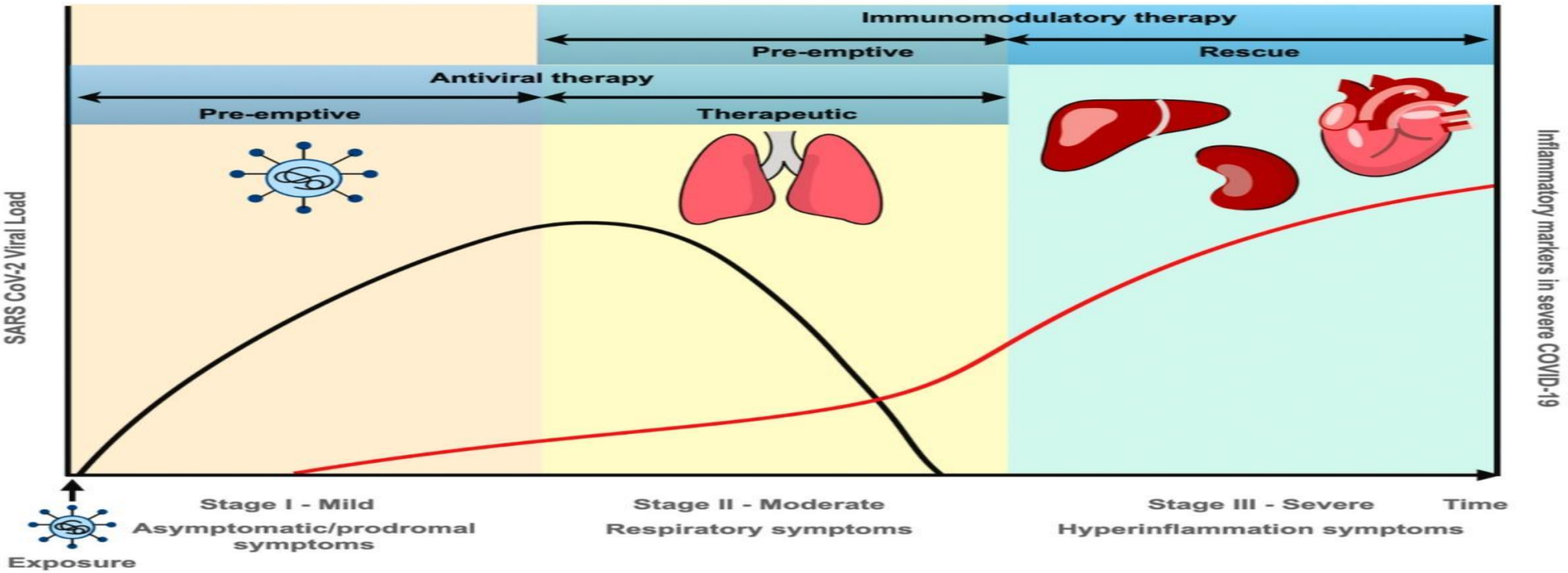
Inflammasomes are activated in response to SARS-CoV-2 infection and are associated with COVID-19 severity in patients

Our results suggest that inflammasomes participate in the pathophysiology of the disease, indicating that these platforms might be a marker of disease severity and a potential therapeutic target for COVID-19.

J. Exp. Med. 2020 Vol. 218 No. 3



Previous studies also reported the activation of NLRP3 inflammasome in COVID-19,which facilitates the initiation of major proinflammatory cytokines, such as IL-1β and IL-18. Therefore, inhibitions of NLRP3 inflammasome and its downstream mediators (eg, IL-1β and IL-18) could potentially reduce COVID-19-associated morbidity and mortality by minimizing the hyperinflammatory state.


Immunomodulatory therapy
Pre-emptive
Rescue
Antiviral therapy
Pre-emptive
Therapeutic
SARS CoV-2 Viral Load
Inflammatory markers in severe COVID-19
Stage I - Mild
Asymptomatic/prodromal symptoms
Stage II - Moderate
Respiratory symptoms
Stage III - Severe
Hyperinflammation symptoms
Time
Exposure

Thank You!