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Evaluation of Cytokine Storm Syndrome and Prevention of Barotrauma and Ventilator-Induced Lung Injury in COVID-19 Acute Respiratory Distress Syndrome

Executive Summary

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Table of Contents

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Evaluation of Cytokine Storm Syndrome and Prevention of Barotrauma and Ventilator-Induced Lung Injury in COVID-19 Acute Respiratory Distress Syndrome

Situation

This review will evaluate the evidence related to Cytokine Storm Syndrome (CSS) and Barotrauma-related Ventilator-Induced Lung Injury (VILI) prevention for severely ill COVID-19 patients with COVID-19 Acute Respiratory Distress Syndrome (CARDS). Additional information is included on the state of practice for CSS and Barotrauma-related VILI prevention for COVID-19 patients with CARDS.

Problem Statement:
Cytokine Storm Syndrome for COVID-19 patients with CARDS requiring intubation can result in devastating barotrauma-related VILI. Does evidence exist to support preventive and treatment therapies for CSS that minimizes the potential need for intubation, subsequently decreasing the risk for VILI as an outcome? What is the current and evolving state of practice for CSS prevention and management, in addition to intubation and ventilation techniques that minimize the risk of barotrauma-related VILI for COVID-19 patients with CARDS?

Technology under Evaluation:
Therapies for treatment of CSS in severely ill COVID-19 patients with CARDS will be addressed, with the goal to minimize the impact of intubation and subsequent risk of barotrauma-related VILI.

Goal(s) of Assessment:

1. Review the literature and evidence related to severely ill COVID-19 patients with CSS and CARDS, and the prevention of barotrauma-related VILI.
2. Report information on the state of practice of CSS management in order to prevent or mitigate barotrauma-related VILI for severely ill COVID-19 patients with CARDS.

Background

COVID-19 disease results from the infection of the SARS-CoV-2 virus. Coronaviruses are RNA viruses that are divided into four genera; alpha-coronaviruses and beta-coronaviruses are known to infect humans. The SARS-CoV-2 virus enters human cells through the angiotensin-converting–enzyme 2 (ACE2) receptor. The SARS-CoV-2 virus structure has RNA-dependent RNA polymerase and proteases, currently targets for drugs that are under investigation as potential treatments for COVID-19 disease. (Gandhi, 2020).

Severe COVID-19 is associated with a cytokine storm characterized by increased plasma concentrations of IL1β, IL2, IL6, IL7, IL8, IL10, IL17, IFNγ, IFNγ-inducible protein 10, monocyte chemoattractant protein 1 (MCP1), G-CSF, macrophage inflammatory protein 1α, and TNFα (Huang, 2020; Zheng, 2020). These inflammatory mediators regulate neutrophil activity and induce the expression of chemo-attractants (molecules that increase the trafficking of neutrophils to sites of inflammation) (Barnes, 2020). Moreover, cytokine storms lead to acute lung injury, ARDS, and death (Channappanavar and Perlman, 2017; Chousterman, 2017).

Cytokine storm syndrome (CSS) and its impact on the respiratory system has been identified as the critical care focus for severe COVID-19 patients. “Cytokines are inflammatory immunologic proteins that are there to fight off infections and ward off cancers. But when they are out of control, they can make you very ill”, as reported by Dr. Robert Cron, a leading COVID-19 researcher (Fortune, 2020). According to Dr. Cron, early reports on the clinical symptoms (fever, confusion) and laboratory features (hyper-ferritinemia, lymphopenia, prolonged pro-thrombin time, elevated lactate dehydrogenase, elevated interleukin (IL) 6, elevated C-reactive protein, and elevated soluble CD25) of severely ill patients with COVID-19, suggest the presence of a cytokine storm syndrome (CSS), resulting in COVID-19 adult respiratory distress syndrome (CARDS) and multi-organ failure.

Ten to fifteen percent of COVID-19 patients progress to acute respiratory distress syndrome (ARDS) triggered by a cytokine storm (Barnes, 2020). Severely ill COVID-19 patients with CSS and CARDS can ultimately progress to require intubation and mechanical ventilation. Barotrauma, which has been used to describe the manifestations of extra-alveolar air during mechanical ventilation, may result due to injury or trauma to the pulmonary system during intubation and mechanical ventilation (Hoo, 2020). Early descriptions of barotrauma refer to the rupture of the lung after forceful exhalation against a closed glottis—for example, pulmonary injury after a deep-sea dive that occasionally is an issue for scuba divers that have ascended or descended too quickly.

Severely ill COVID-19 patients with CSS and CARDS, are susceptible to barotrauma during intubation and mechanical ventilation, resulting in ventilator-induced lung injury (VILI). VILI develops in severely ill COVID-19 patients because high transpulmonary pressure during mechanical ventilation induces stress across the lung that is poorly tolerated in CARDS. Ventilator management for COVID-19 patients with CARDS requires relatively low tidal volumes, together with tolerance for modest (permissive) hypercapnia, to facilitate the goal of minimizing ventilator-induced lung injury (VILI) (Marini, 2020).

This report will review findings on CSS and CARDS therapies that may contribute to the prevention of barotrauma and VILI for CARDS patients with severe COVID-19. Ongoing evaluation of potential therapies for CSS to prevent barotrauma-related VILI for CARDS patients with severe COVID-19 is necessary, given the limited amount of studies that have been conducted to date. Findings discovered to date are summarized in the following sections.

Assessment

A review of the published literature to determine the evidence related to the prevention of CSS and management of CARDS to mitigate VILI are presented in the following sections. Below we have identified the following guidelines and position statements related to CSS in patients with CARDS and VILI.

Position Statements and Guidelines:

Table 1. Clinical Guidelines/Practice Statement

Name of Organization	Date Searched	Guidance Identified
National Institutes of Health: COVID-19 Treatment Guidelines	April 27, 2020	Link provided.
Centers for Disease Control and Prevention (CDC)		
Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19)	April 29, 2020	Link provided.
World Health Organization (WHO)		
WHO INTERIM GUIDANCE DOCUMENT: Clinical Management of Acute Respiratory Distress Syndrome in Patients with suspected Novel Coronavirus Disease	April 30, 2020	Link provided.
Infectious Disease Society of America		
Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19	April 30, 2020	Link provided.
Society of Critical Care Medicine		
SCCM Guidance: Surviving Sepsis Campaign	April 30, 2020	Link provided.

Guidelines

1. National Institutes of Health - COVID-19 Treatment Guidelines: Critical Care

Infection Control:

- For health care workers who are performing aerosol-generating procedures on patients with COVID-19, the COVID-19 Treatment Guidelines Panel (the Panel) recommends using fit-

tested respirators (N-95 respirators) or powered air-purifying respirators rather than surgical masks, in addition to other personal protective equipment (i.e., gloves, gown, and eye protection such as a face shield or safety goggles) **(AIII)**.
- The Panel recommends that endotracheal intubation for patients with COVID-19 be done by health care providers with extensive airway management experience, if possible **(AIII)**.
- The Panel recommends that intubation be achieved by video laryngoscopy, if possible**(CIII)**.

Hemodynamic Support:

- The Panel recommends norepinephrine as the first-choice vasopressor **(AII)**.
- The Panel recommends using dobutamine in patients who show evidence of persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents **(BII)**.

Ventilatory Support:

- For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, the Panel recommends high-flow nasal cannula (HFNC) oxygen over noninvasive positive pressure ventilation (NIPPV) (BI).
- In the absence of an indication for endotracheal intubation, the Panel recommends a closely monitored trial of NIPPV for adults with COVID-19 and acute hypoxemic respiratory failure for whom HFNC is not available (BIII).
- For adults with COVID-19 who are receiving supplemental oxygen, the Panel recommends close monitoring for worsening of respiratory status and recommends early intubation by an experienced practitioner in a controlled setting (AII).
- For mechanically ventilated adults with COVID-19 and acute respiratory distress syndrome (ARDS), the Panel recommends using low tidal volume (Vt) ventilation (Vt 4–8 mL/kg of predicted body weight) over higher tidal volumes (Vt >8mL/kg) **(AI)**.
- For mechanically ventilated adults with COVID-19 and refractory hypoxemia despite optimized ventilation, the Panel recommends prone ventilation for 12 to 16 hours per day over no prone ventilation **(BII)**.
- For mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia despite optimized ventilation and other rescue strategies, the Panel recommends a trial of inhaled pulmonary vasodilator as a rescue therapy; if no rapid improvement in oxygenation is observed, the patient should be tapered off treatment **(CIII)**.
- There are insufficient data to recommend either for or against the routine use of extracorporeal membrane oxygenation for patients with COVID-19 and refractory hypoxemia **(BIII)**.

Drug Therapy:

- There are insufficient data for the Panel to recommend either for or against any antiviral or immunomodulatory therapy in patients with severe COVID-19 disease (AIII).

- In patients with COVID-19 and severe or critical illness, there are insufficient data to recommend empiric broad-spectrum antimicrobial therapy in the absence of another indication (BIII).
- The Panel recommends against the routine use of systemic corticosteroids for the treatment of mechanically ventilated patients with COVID-19 without ARDS (BIII).
- In mechanically ventilated adults with COVID-19 and ARDS, there are insufficient data to recommend either for or against corticosteroid therapy in the absence of another indication (CI).
- In COVID-19 patients with refractory shock, low-dose corticosteroid therapy is preferred over no corticosteroid therapy (BII).

Clinical Studies

A review of existing studies related to the CSS management and the prevention of VILI for severely ill COVID-19 patients with CARDS is provided in Table 2. Given the short history of COVID-19, there are relatively few clinical studies that are able to report findings for COVID-19 therapies. Although we were able to include in our review are recent findings reported from the ongoing Adaptive COVID-19 Treatment Trial and efficacious of Remdesivir. This information is included in summary of the relevant study literature identified to date below in Table 2.

Table 2. Summary of Study Methods and Findings

Keywords: CSS, cytokine storm syndrome; CRS, cytokine release storm; CoV, coronavirus; Remdesivir; SARS-COV-2; COVID-19; IVIG; clinical efficacy; mortality; ARDS, Acute Respiratory Disease Syndrome; ELISA; mechanical ventilation; VILI; Ventilator-induced lung injury; barotrauma; CARDS, COVID-19 Acute Respiratory Disease Syndrome; neutrophilia.

Authors/Study Design	Study Population	Treatment	Results	Key Findings/ Strengths/Limitations Individual Study Quality*
National Institutes of Health, US National Institute of Allergy and Infectious Disease; Adaptive COVID-19 Treatment Trial Adaptive, randomized, double-blind, placebo-controlled trial Dates: February 21, 2020, to April 19, 2020; final follow-up 29 days from last date of enrollment (May 9, 2020)	n=1063 critically ill patients with COVID-19 and acute respiratory distress syndrome (ARDS), meeting following criteria: 1. Laboratory-confirmed SARS-CoV-2 infection 2. Evidence of lung involvement, including: i) Rales (rattling sounds when breathing)	Patients in the investigational treatment group will receive: 1. 200 milligrams (mg) of remdesivir intravenously on 1st day of study enrollment; 2. Another 100 mg each day for the duration of hospitalization, for up to 10 days total. Placebo group received, at an equal volume, a solution that resembles	Results demonstrated: 1. 31% faster recovery time for remdesivir treatment group compared with placebo group (P <.001). 2. 11 day recovery for remdesivir treatment group compared with 15 day recovery for placebo group. 3. Survival benefit, of 8.0% mortality rate remdesivir treatment group versus 11.6% for the placebo group (P = .059).	Preliminary findings released on April 29, 2020 by US National Institute of Allergy and Infectious Diseases (NIAD) suggests treatment with remdesivir better than placebo based on primary endpoint, time to recovery. *Strengths:* • Randomized, doubled-blinded trial *Limitations*: • Limited sample size • Ongoing study; data incomplete

Authors/Study Design	Study Population	Treatment	Results	Key Findings/ Strengths/Limitations Individual Study Quality*
Funding Source: National Institutes of Health/ US National Institute of Allergy and Infectious Diseases (NIAD)	ii) Need for supplemental oxygen; iii) Abnormal chest X-rays; or iv) Illness requiring mechanical ventilation.	remdesivir but contains only inactive ingredients.		*Conflicts of Interest*: None stated
Wu C et al., 2020 Single site in Wuhan, China Retrospective, cohort study to evaluate the contributing risk factors for COVID-19 pneumonia patients that progress to ARDS and ARDS to death Clinical Registry Identifier: NR Time Duration: 33 days Time Frame: December, 25 2019 through January 26, 2020. Funding Source: NR	n=201 pts with confirmed COVID-19 pneumonia, admitted to Wuhan Jinyintan Hospital in China. Power analysis: Not reported Inclusion criteria: COVID-19 pneumonia patient Exclusion criteria: NR Clinical hx/pt. characteristics: Mean age (yrs): 51 ±8 % male: 63.7%	Recruitment and design Retrospective analysis of COVID-19 pts treated for pneumonia, developing ARDS and ARDS progressing to death in the defined study time span.	F/U and retention: NA Clinical Outcomes Eighty-four patients (41.8%) developed ARDS, and of those 84 patients, 44 (52.4%) died. Patients who developed ARDS presented with dyspnea (50 of 84 [59.5%] vs 30 of 117 [25.6%] patients who did not develop ARDS. Comorbidities for COVID-19 pneumonia who developed pneumonia and those who did not included, hypertension (23 of 84 [27.4%] patients who developed ARDS and 16 of 117 [13.7%] patients, and diabetes (16 of 84 [19.0%] patients and 6 of 117 [5.1%] patients respectively. Risk factors associated with the development of ARDS and progression from ARDS to death included older age (hazard ratio [HR], 3.26; 95% CI 2.08-5.11; and HR, 6.17; 95% CI, 3.26-11.67, respectively), neutrophilia (HR, 1.14; 95% CI, 1.09-1.19; and	Results suggest risks factors for COVID-19 pneumonia patients progression to the development of ARDS and progression from ARDS to death include: • Older age • Neutrophilia • Organ and coagulation dysfunction High fever associated to higher likelihood of ARDS, but lower likelihood of deaths. Treatment with methylprednisolone may be beneficial in preventing death for patients who develop ARDS. Strengths: • Only identified study for COVID-19 pneumonia patients focused on ARDS and progression to death Limitations: • Retrospective • Small sample size • Single site • No scheduled f/u to date

Authors/Study Design	Study Population	Treatment	Results	Key Findings/ Strengths/Limitations Individual Study Quality*
			HR, 1.08; 95% CI, 1.01-1.17, respectively), and organ and coagulation dysfunction (eg, higher lactate dehydrogenase [HR, 1.61; 95% CI, 1.44-1.79; and HR, 1.30; 95% CI, 1.11-1.52, respectively] and D-dimer [HR, 1.03; 95% CI, 1.01-1.04; and HR, 1.02; 95% CI, 1.01-1.04, respectively]). High fever (≥39 °C) was associated with higher likelihood of ARDS development (HR, 1.77; 95% CI, 1.11-2.84) and lower likelihood of death (HR, 0.41; 95% CI, 0.21-0.82. Patients with ARDS, treatment with methylprednisolone, decreased the risk of death (HR, 0.38; 95% CI, 0.20-0.72)	Conflicts of Interest: None identified.

State of Practice

Based on the literature reviewed, findings on the state of practice for the CARDS ventilation management to support mitigation of barotrauma-related VILI are presented in Table 3 and the state of practice for CSS for COVID-19 patients with CARDS in Table 4 below. Included in the review are the recent recommendations for CARDS ventilation management, based on findings published in JAMA on April 26, 2020. Ongoing monitoring of the literature is recommended as information is being published to reflect the evolving understanding of COVID-19.

Table 3. State of Practice Observations for CARDS Ventilation Management

Table. Time Course and Treatment Approach to Ventilation Support for Patients With CARDS

Time period	Objective	Respiratory support options	Rationale
Before intubation	Adequate gas exchange Avoid P-SILI	Supplemental oxygen, CPAP, NIV, HFNC Awake prone positioning, Target nonvigorous breathing	Powerful respiratory effort can cause reinforcing lung and vascular stress, resulting in injury
During mechanical ventilation	Avoid pulmonary deterioration and VILI vortex	Minimize PEEP, frequency and tidal volume Adjust to acceptable gas exchange Maintain fluid balance Reduce O_2 demand Consider ECMO	Minimize transpulmonary and vascular stresses
After intubation	Minimize pulmonary stress Optimize O_2 Avoid VILI vortex	Type L[a]: use lower PEEP (<10 cm H_2O) Use more liberal tidal volume (7-9 mL/kg) as needed Reduce O_2 demand Consider prone positioning	Lower tidal volumes are unnecessary Higher PEEP is ineffective, creates dead space, and adversely redirects blood flow
	Reduce and evenly distribute lung and vascular stresses Optimize O_2 Avoid VILI vortex	Type H[a]: use higher PEEP (<15 cm H_2O) Lower tidal volume (5-7 mL/kg) Reduce O_2 demand Implement prone positioning	More closely behaves and responds like typical ARDS
Weaning phase	Avoid reversion to previously worsened pulmonary state by causing VILI and worsening edema	Make transitions cautiously Avoid abrupt changes Spontaneous trials only at the very end of the weaning process	Strong spontaneous efforts raise O_2 demand, increase edema, and promote P-SILI

Abbreviations: ARDS, acute respiratory distress syndrome; CARDS, COVID-19 with ARDS; CPAP, continuous positive airway pressure; ECMO, extracorporeal membrane oxygenation; HFNC, high-flow nasal cannula; NIV, noninvasive ventilation; P-SILI, patient self-inflicted lung injury; PEEP, positive end-expiratory pressure; VILI, ventilator-induced lung injury.

[a] Type L: Scattered ground-glass infiltrates, higher compliance (>50 mL/cm H_2O), not PEEP responsive; less dyspnea.
Type H: Extensive infiltrates of atelectasis and edema, lower compliance, PEEP responsive, overtly dyspneic.

SOURCE: Marini J and Gattinoni L; JAMA, 2020.

Table 4. State of Practice Observations for CSS management and the prevention of VILI

Phase	Therapy	Observation	SOP Implication	Source/Organization
Experimental/ National Cancer Institute study	Bruton's tyrosine kinase (BTK) inhibitor, Acalabrutinib	Acalabrutinib (trade name Calquence, AstraZeneca) is FDA approved drug that blocks the BTK protein that is key to the signaling of white blood B cells of the human immune system into action. Acalabrutinib has been proven to be especially effective in	National Cancer Institute study ACE-ID- 201, A Phase 2 Randomized Study of the Efficacy and Safety of Acalabrutinib With Best Supportive Care Versus Best Supportive Care in Subjects Hospitalized With COVID-19 Study objective is to investigate the safety, efficacy and pharmacokinetics of acalabrutinib together with Best Supportive Care in	National Library of Medicine, 2020

		patients with chronic lymp.	the treatment of COVID-19. Ongoing monitoring of results of study ACE-ID-201 is necessary to evaluate findings and potential treatment of COVID-19.	
Experimental/ National Institutes of Health	High Dose Intravenous Vitamin C (HDIVC)	Researcher have initiated a trial on April 22, 2020 to evaluate whether the administration of HDIVC at the first objective sign of worsening oxygenation, as documented by change in peripheral capillary oxygen saturation (SpO2) to fraction of inspired oxygen (FIO2) ratio (S/F) or decreased SpO2 at baseline (mild hypoxia group), may reduce the inflammatory process and development of respiratory failure requiring intubation. Included in study results after administration of HDIVC are the results of inflammatory markers that are elevated in COVID-19 (d-dimer, CRP, LDH, liver enzymes, and ferritin) to develop a mechanistic understanding and risk stratification of response to HDIVC infusion.	National Institutes of Health Trial NCT04357782, Administration of Intravenous Vitamin C in Novel Coronavirus Infection and Decreased Oxygenation (AVoCaDO) Phase I/II Safety, Tolerability, and Efficacy Clinical Trial Ongoing monitoring of results of study NCT04357782 is necessary to evaluate findings and potential treatment of COVID-19.	National Library of Medicine, 2020
Academic research/ Massachusetts Institute of Technology (MIT)	QTY code-designed water-soluble Fc-fusion cytokine receptors	Application of the QTY code on six variants of cytokine receptors, including interleukin receptors IL4αR and IL10αR, chemokine receptors	Cytokine receptor-Fc fusion proteins serve as an antibody-like decoy to dampen the excessive cytokine levels associated	Hao C, 2020

		CCR9 and CXCR2, as well as interferon receptors IFNγR1 and IFNλR1. QTY- variant cytokine receptors resulted in water-soluble fusion receptors, able to bind to their respective ligands with Kd values affinity similar to isolated native receptors.	with CRS and COVID-19 infection. MIT researchers findings target cytokine storms seen in COVID-19 patients by designing antibody-like receptor proteins that can bind to cytokines, as possible strategy for treating coronavirus and other infections. Ongoing monitoring of MIT findings is necessary to evaluate findings and potential treatment of COVID-19.	
Academic research/ NETwork institutions	Neutrophil extracellular traps (NETs)	NETs are web-like structures of DNA and proteins expelled from the neutrophil that ensnare pathogens. Although NETs are beneficial in the host defense against pathogens, collateral damage from sustained NET formation also stimulates many disease processes, including those that occur during viral infections Excessive NET formation can trigger a cascade of inflammatory reactions that promotes cancer cell metastasis, destroys surrounding tissues, facilitates microthrombosis, and results in permanent organ damage to the pulmonary, cardiovascular, and renal systems, commonly affected	Experiments are evaluating how neutrophilia could be a source of excess neutrophil extracellular traps (NETs). If NETs are shown to cause the severe symptoms of COVID-19, new avenue for treatment approaches. Potential to repurpose drugs used in other NET and neutrophil-driven diseases, such as cystic fibrosis, gout and rheumatoid arthritis. Ongoing monitoring NETwork institutions findings is necessary to evaluate findings and potential treatment of COVID-19.	Barnes B, 2020

		organ systems in severe COVID-19.		
Experimental	Sarilumab	Interleukin-6 (IL-6) receptor inhibitor. May be helpful in reducing lung inflammation and improving lung function.	Cytokine directed approach. Helpful in genetic-based CSS; further evaluation of genetic disposition and COVID-19 is necessary.	FDA News Release, March 29, 2020
FDA-approved, Compassionate Care use	Remdesivir	Antiviral agent that was initially trialed thru compassionate care studies that showed impact on COVID-19 patients severely ill. FDA approved for Emergency Use Authorization on May 2020.	Severely ill COVID-19 patients included in trial demonstrated 1% faster time to recovery, 11 days vs 15 days for placebo group; survival benefit, with a mortality rate of 8.0% vs 11.6% for placebo group.	NIH News Releases, April 29, 2020
Contraindicated Treatment	Corticosteroids	Initially considered for treatment of patients with severe illness, for possible benefit by reducing inflammatory-induced lung injury. Subsequent evaluation suggested that corticosteroids did not have an effect on mortality, but rather delayed viral clearance. Patients with MERS-CoV or influenza given corticosteroids more likely to have prolonged viral replication, receive mechanical ventilation, and have higher mortality.	Corticosteroids should be avoided unless indicated for other reasons, such as management of chronic obstructive pulmonary disease exacerbation or septic shock, according to WHO interim guidelines and updated CDC guidelines.	Huang L, 2019 World Health Organization, Interim Guidelines for COVID-19 Center for Disease Control Guidelines, COVID-19 Disease

Summary

Literature was reviewed on the management of CSS and the prevention of barotrauma-related VILI for CARDS patients with severe COVID-19. The clinical studies reviewed current state for therapies that are currently being evaluated, recognizing that the pipeline of therapies under investigation will determine future therapies. JAMA Ventilation Management guidelines focus on appropriate to minimal Positive End Expiratory Pressure (PEEP) support for CARDS. Specifically, lower PEEP settings that are less than 10 cm H2O are recommended to minimize the amount of dead space created by mechanical ventilation (Marini and Gattinoni, 2020). Regarding the state of practice for CSS and barotrauma-related VILI, therapies targeting the eradication of the virus are the primary modality for therapies under development. As promising as these therapies may appear, it is important to recognize that there is only one approved therapy for the treatment of COVID-19, Remdesivir, which has been approved for by the FDA as an Emergency Use Authorization therapy on May 1st, 2020.

Given the current state of practice and ongoing acquisition of evidence and data, ongoing monitoring of future literature publications is necessary.

Abstracts

Clinical and biological implications of target occupancy in CLL treated with the BTK inhibitor acalabrutinib

Sun C et al. Blood. 2020 Mar 20. pii: blood.2019003715. doi: 10.1182/blood.2019003715. [Epub ahead of print]

Inhibition of the B-cell receptor pathway, and specifically of Bruton tyrosine kinase (BTK), is a leading therapeutic strategy in B-cell malignancies, including chronic lymphocytic leukemia (CLL). Target occupancy is a measure of covalent binding to BTK and has been applied as a pharmacodynamic parameter in clinical studies of BTK inhibitors. However, the kinetics of de novo BTK synthesis, which determines occupancy, and the relationship between occupancy, pathway inhibition and clinical outcomes remain undefined. This randomized phase 2 study investigated the safety, efficacy, and pharmacodynamics of a selective BTK inhibitor acalabrutinib at 100 mg twice daily (BID) or 200 mg once daily (QD) in 48 patients with relapsed/refractory or high-risk treatment naïve CLL. Acalabrutinib was well tolerated and yielded an overall response rate (ORR) of partial response or better of 95.8% (95% CI 78.9%, 99.9%) and an estimated progression-free survival (PFS) rate at 24 months of 91.5% (95% CI 70.0%, 97.8%) with BID dosing and an ORR of 79.2% (95% CI 57.9%, 92.9%) and an estimated PFS rate at 24 months of 87.2% (95% CI 57.2%, 96.7%) with QD dosing. BTK re-synthesis was faster in CLL than in healthy volunteers. BID dosing maintained higher BTK occupancy and achieved more potent pathway inhibition compared to QD dosing. Small increments in occupancy attained by BID dosing relative to QD dosing compounded over time to augment

downstream biological effects. The impact of BTK occupancy on long-term clinical outcomes remains to be determined.

QTY code-designed water-soluble Fc-fusion cytokine receptors bind to their respective ligands

Hao S et al. Massachusetts Institute for Technology. Accepted Manuscript for QRB Discovery, as part of the Cambridge Coronavirus Collection. DOI: 10.1017/qrd.2020.4

Cytokine release syndrome (CRS), or “cytokine storm”, is the leading side effect during CAR-T therapy that is potentially life-threatening. It also plays a critical role in viral infections such as COVID-19. Therefore, efficient removal of excessive cytokines is essential for treatment. We previously reported a novel protein modification tool called the QTY code, through which hydrophobic amino acids Leu, Ile, Val and Phe are replaced by Gln (Q), Thr (T) and Tyr (Y). Thus, the functional detergent-free equivalents of membrane proteins can be designed. Here we report the application of the QTY code on six variants of cytokine receptors, including interleukin receptors IL4αR and IL10αR, chemokine receptors CCR9 and CXCR2, as well as interferon receptors IFNγR1 and IFNλR1. QTY- variant cytokine receptors exhibit physiological properties similar to those of native receptors without the presence of hydrophobic segments. The receptors were fused to the Fc region of IgG protein to form an antibody-like structure. These QTY code-designed Fc fusion receptors were expressed in E. coli and purified. The resulting water-soluble fusion receptors bind to their respective ligands with Kd values affinity similar to isolated native receptors. Our cytokine receptor-Fc fusion proteins potentially serve as an antibody-like decoy to dampen the excessive cytokine levels associated with CRS and COVID-19 infection.

Neutrophil extracellular traps

Barnes B et al. J *Exp Med* (2020) 217 (6): e20200652. https://doi.org/10.1084/jem.20200652.

Coronavirus disease 2019 (COVID-19) is a novel, viral-induced respiratory disease that in ∼10–15% of patients progresses to acute respiratory distress syndrome (ARDS) triggered by a cytokine storm. In this Perspective, autopsy results and literature are presented supporting the hypothesis that a little known yet powerful function of neutrophils—the ability to form neutrophil extracellular traps (NETs)—may contribute to organ damage and mortality in COVID-19. We show lung infiltration of neutrophils in an autopsy specimen from a patient who succumbed to COVID-19. We discuss prior reports linking aberrant NET formation to pulmonary diseases, thrombosis, mucous secretions in the airways, and cytokine production. If our hypothesis is correct, targeting NETs directly and/or indirectly with existing drugs may reduce the clinical severity of COVID-19.

Compassionate Use of Remdesivir for Patients with Severe Covid-19.

Grein J et al. www.nejm.org. n engl j med. Accessed April 15, 2020. April 10, 2020. DOI: 10.1056/NEJMoa2007016

Background: Remdesivir, a nucleotide analogue prodrug that inhibits viral RNA polymerases, has shown in vitro activity against SARS-CoV-2.

Methods: We provided remdesivir on a compassionate-use basis to patients hospitalized with Covid-19, the illness caused by infection with SARS-CoV-2. Patients were those with confirmed SARS-CoV-2 infection who had an oxygen saturation of 94% or less while they were breathing ambient air or who were receiving oxygen support. Patients received a 10-day course of remdesivir, consisting of 200 mg administered intravenously on day 1, followed by 100 mg daily for the remaining 9 days of treatment. This report is based on data from patients who received remdesivir during the period from January 25, 2020, through March 7, 2020, and have clinical data for at least 1 subsequent day.

Results: Of the 61 patients who received at least one dose of remdesivir, data from 8 could not be analyzed (including 7 patients with no post-treatment data and 1 with a dosing error). Of the 53 patients whose data were analyzed, 22 were in the United States, 22 in Europe or Canada, and 9 in Japan. At baseline, 30 patients (57%) were receiving mechanical ventilation and 4 (8%) were receiving extracorporeal membrane oxygenation. During a median follow-up of 18 days, 36 patients (68%) had an improvement in oxygen-support class, including 17 of 30 patients (57%) receiving mechanical ventilation who were extubated. A total of 25 patients (47%) were discharged, and 7 patients (13%) died; mortality was 18% (6 of 34) among patients receiving invasive ventilation and 5% (1 of 19) among those not receiving invasive ventilation.

Conclusion: In this cohort of patients hospitalized for severe Covid-19 who were treated with compassionate-use remdesivir, clinical improvement was observed in 36 of 53 patients (68%). Measurement of efficacy will require ongoing randomized, placebo-controlled trials of remdesivir therapy. (Funded by Gilead Sciences.)

Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology

Channappanavar R and Perlman S. Semin Immunopathol. 2017 Jul;39(5):529-539. doi: 10.1007/s00281-017-0629-x. Epub 2017 May 2.

Human coronaviruses (hCoVs) can be divided into low pathogenic and highly pathogenic coronaviruses. The low pathogenic CoVs infect the upper respiratory tract and cause mild, cold-like respiratory illness. In contrast, highly pathogenic hCoVs such as severe acute respiratory syndrome CoV (SARS-CoV) and Middle East respiratory syndrome CoV (MERS-CoV) predominantly infect lower airways and cause fatal pneumonia. Severe pneumonia caused by pathogenic hCoVs is often associated with rapid virus replication, massive inflammatory cell infiltration and elevated pro-inflammatory cytokine/chemokine responses resulting in acute lung

injury (ALI), and acute respiratory distress syndrome (ARDS). Recent studies in experimentally infected animal strongly suggest a crucial role for virus-induced immunopathological events in causing fatal pneumonia after hCoV infections. Here we review the current understanding of how a dysregulated immune response may cause lung immunopathology leading to deleterious clinical manifestations after pathogenic hCoV infections.

NETs by-products and extracellular DNA may play a key role in COVID-19 pathogenesis: incidence on patient monitoring and therapy

Thierry, A and Roch B. NETs By-products and Extracellular DNA May Play a Key Role in COVID-19 Pathogenesis: Incidence on Patient Monitoring and Therapy. *Preprints* 2020, 2020040238 (doi: 10.20944/preprints202004.0238.v1).

Neutrophils play an important role as the first line of innate immune defense. One function of neutrophils, called neutrophil extracellular traps (NETs), has been discovered recently. NETs are extensive fibrous structures released extracellularly from activated neutrophils in response to infection. They are composed of cytosolic protein assembled on a scaffold of released chromatin. These structures suppress the dissemination of micro-organisms in blood by trapping them mechanically, and by exploiting coagulant function to segregate them within the circulation. In addition, NET components (DNA, histone, and granule proteins) also contribute to the triggering of an inflammatory process. NET function, however, can be regarded as a double-edged sword. On one hand, NET formation is an efficient strategy for neutralizing invading micro-organisms. On the other hand, NET can be harmful to the host, as its exposed by-products that are toxic to endothelial cells and parenchymal tissue. We present here the analogous biological and physiological features of the harmful positive amplification loop between inflammation and tissue damage induced by NETosis dysregulation and Coronavirus Disease-2019 (COVID-19) pathogenesis. Considering the rapid evolution of this disease symptoms and its lethality, we hypothesize that COVID-19 progresses under an amplifier loop, leading to a massive, uncontrolled inflammation process. We also describe the correlations of COVID-19 symptoms and biological features with those consecutive to uncontrolled NET formation causing various sterile or infectious diseases. General clinical conditions, and numerous pathological and biological features, are analogous with NETs deleterious effects. We postulate that Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV2) induces a disproportionate virus-induced NET release, and that this plays a key role in COVID-19 pathogenesis. While neutrophils are the principal starting point for extracellular and circulating DNA release, targeting NETs rather than neutrophils themselves may stand for an effective strategy. This paper offers an in-depth review of NET formation, function and pathogenic dysregulation, as well as of current and future therapies to control NET unbalance. As such, it enables us also to suggest new therapeutic strategies to fight COVID-19. In combination with or independent of the latest tested approaches, we propose that, in the short term,

deoxyribonuclease I (DNase-1) treatment should be evaluated; we also advocate a significant increase in research on the development of toll-like receptors (TLR) and C-type Lectin like receptors (CLEC) inhibitors, and on anti-IL26 therapies.

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