

New Decade, Old Debate: Blocking the Cytokine Pathways in Infection-Induced Cytokine Cascade

OBJECTIVES: Our understanding of the immunopathogenesis of coronavirus disease 2019 is evolving; however, a “cytokine storm” has been implicated. Ongoing clinical trials are evaluating the value of anticytokine therapies to treat patients with coronavirus disease 2019. This review summarizes the existing literature evaluating the efficacy and safety of anticytokine therapy to tackle the dysregulated immune response to infectious pathogens, discusses potential reasons for failure, applicability to coronavirus disease 2019, and future direction.

DATA SOURCES: Medline, PubMed, ClinicalTrials.gov, and media reports.

STUDY SELECTION: The studies were included by author consensus.

DATA EXTRACTION: Data were selected for inclusion after reviewing each study by author consensus.

DATA SYNTHESIS: “Cytokine storm” is a nonspecific term, encompassing systemic inflammatory response to infectious pathogens, autoimmune conditions, cancers, trauma, and various chemotherapies. Like bacterial sepsis, viral pathogens may fuel immunopathogenesis by inducing a dysregulated autoamplifying cytokine cascade, ultimately leading to organ injury. This narrative review discusses what we know of the immune milieu of coronavirus disease 2019 versus noncoronavirus disease 2019 sepsis and/or acute respiratory distress syndrome, summarizes the existing literature on cytokine inhibitors in patients with sepsis and/or acute respiratory distress syndrome, and discusses possible reasons for recurrent failure. In doing so, it aims to assist decisions regarding the use of anticytokine therapy in patients with coronavirus disease 2019, as many regions of the world confront the second wave of the pandemic.

CONCLUSIONS: As ongoing clinical trials determine the efficacy and safety of anticytokine therapy in patients with coronavirus disease 2019, clinicians should uphold caution when incorporating it into treatment protocols, while maintaining focus on established evidence-based practices and the mantra of “less is more.”

KEY WORDS: coronavirus disease 2019; cytokine inhibition; cytokine storm; sepsis; tocilizumab

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DOI: 10.1097/CCE.0000000000000364

Coronavirus disease 2019 (COVID-19) has affected over 100 million people worldwide and killed more than 2 million people by January 29, 2021 (1).

Early case series of COVID-19 reported elevated levels of plasma cytokines in infected patients, arbitrarily described as the “cytokine storm”. Globally, this

resurfaced interest in cytokine antagonists and cytokine clearance as treatment options for COVID-19. However, history upholds that these seemingly exceptional increments in systemic cytokines in patients with COVID-19 are not unusual in human hosts responding to an infectious pathogen and may actually be trivial as compared to patients with non-COVID-19 acute respiratory distress syndrome (ARDS) or sepsis (2). Archived literature also stands witness to the nonperformance of indiscriminate immunomodulation in sepsis and/or ARDS (Table 1).

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection (19, 20). Cytokine release syndrome (CRS) is an unrestricted systemic inflammatory response to immunotherapy, first reported in the early 1990s with chimeric antigen receptor (CAR) T-cell therapy. “Cytokine storm” has no definition. It has been adopted as a nonspecific umbrella term loosely encompassing a spectrum of systemic inflammatory syndromes involving elevated levels of circulating cytokines leading to varying severity of organ dysfunction and can be triggered by infectious pathogens, autoimmune conditions, cancers, trauma, surgery, and various therapies (21). Distinctive systemic cytokine profiles for each subcategory are yet to be fully elucidated; however, emerging data suggest that the median cytokine increments in severe and critical COVID-19 are underwhelming compared with the cytokine profiles in non-COVID sepsis and ARDS and incomparable with the massive cytokine release in CRS (2). Although the pathophysiology of COVID-19 is being elucidated, there is a keen and sustained interest in immunotherapy for COVID-19, with numerous clinical trials lined up to investigate various cytokine inhibitors.

The idea of neutralizing the “cytokine storm” induced by infections, using cytokine pathway inhibitors or cytokine removal, is not novel. In this review, we will discuss the decades-long grim history of pharmacologic and nonpharmacologic anticytokine therapies in bacterial sepsis and/or ARDS, both conditions with evidently more pronounced systemic cytokine release than severe and critical COVID-19 (2). Although conceptually promising, with proven effectiveness in attenuating the inflammatory response in some animal models, in human trials, these approaches have been either inconclusive, failed

to improve outcomes, or portended harm (22–25) (Table 1 and Fig. 1).

EVIDENCE BEHIND ANTI-CYTOKINE THERAPY IN SEPSIS AND/OR ARDS

Interleukin-1 Inhibition

Three decades ago, the use of interleukin-1 receptor antagonist (IL-1ra) therapy in sepsis was conceptualized to counteract the dysregulated immune response induced by overwhelming infections and potentially decrease the occurrence of multiple organ failure and improve outcome. IL-1ra prevents interleukin (IL)-1 mediated cellular responses by competitively and reversibly occupying the receptors for IL-1 (26). As with many preliminary studies, a small phase II clinical trial in patients with sepsis demonstrated a marked 28-day survival benefit with recombinant human IL-1ra (rhIL-1ra) treatment (3). In a multinational, double-blind, randomized controlled trial (RCT) to evaluate the efficacy of rhIL-1ra on mortality in patients with “tachycardia-tachypnea-fever” and hypotension or end-organ dysfunction due to an infection, rhIL-1ra failed to demonstrate a benefit in 28-day survival but on retrospective analysis showed some positive effects among the most severe patients (4). A confirmatory trial among patients with severe sepsis or septic shock was stopped early for futility (8). Revisited this decade, CORIMUNO-ANA-1 was stopped early for futility as rhIL-1ra failed to improve outcomes in mild-moderate COVID-19 (27).

Tumor Necrosis Factor- α Inhibition

Tumor necrosis factor (TNF)- α is essential to the generation of both innate and acquired immune responses to an infectious challenge. In the late 1980s, it was demonstrated that administration of *Escherichia coli* endotoxin to human volunteers results in a brief pulse of circulating TNF with consequent fever, tachycardia, and increase in circulating stress hormones (28). Administration of TNF to dogs resulted in hemodynamic collapse and critical organ injury (29). In subsequent animal studies, neutralizing the effects of circulating TNF resulting from bacteremia successfully obviated shock and vital organ injury (30). Three decades ago, in a multicenter, double-blind RCT, administration of a neutralizing TNF- α receptor:Fc fusion protein in patients with septic shock did not

reduce mortality, with higher doses associated with a statistically significant increase in mortality (6). This study was criticized due to the legitimate concern that only a small proportion of patients (4%) had any detectable circulating TNF- α levels at baseline. Despite preventing death in animal models of sepsis and septic shock and showing a reduction in mortality in a phase II trial among patients with severe sepsis and early septic shock (< 4 hr of vasopressors), in a multicenter RCT of 1,342 patients with severe sepsis and early septic shock and detectable baseline TNF- α levels, Lenercept (a p55 TNF receptor fusion protein) did not reduce mortality (9, 11, 31).

Toll-Like Receptor Inhibition

Infecting microbes express macromolecules termed pathogen-associated molecular patterns (PAMPs) on their surface (lipopolysaccharides [LPS], peptidoglycans, etc.). When these are recognized by pattern recognition receptors (toll-like receptor [TLR]) on the surface of immune cells, host immune response is initiated. This results in the synthesis and release of pro-inflammatory cytokines such as TNF- α , IL-1, IL-6, and IL-8. TLR-4 inhibition results in suppression of TLR-4 mediated cytokine cascade to LPS challenge in vitro and in animal studies (32, 33). However, inhibition of TLR-4 with an antagonist TAK-242 (Resatorvid) in patients with severe sepsis and shock or respiratory failure failed to suppress cytokine levels or reduce mortality (12). Among 1,984 patients with severe sepsis and septic shock, the use of Eritoran (a TLR-4 inhibitor), compared with placebo, did not result in reduction of 28-day mortality or reduction in cytokine levels (13). This failure to obviate the cytokine cascade by TLR-4 specific inhibition may be due to redundancies in the inflammatory signaling system (12). In addition, although TLR-4 detects LPS, other important bacterial, viral, or parasitic PAMPs are ligands for alternative TLR family members which may explain the nonperformance of TLR-4-specific inhibitors in an indiscriminate cohort of septic patients (34).

IL-6 Inhibition

Tocilizumab, an IL-6 inhibitor, is approved for the treatment of patients with severe or life-threatening CRS due to CAR T-cell therapy. With the search of a scalable treatment measure as top priority, the benefits

of IL-6 inhibitors seen in CRS were arbitrarily extrapolated to COVID-19. However, crucial factors set apart CRS from COVID-19: its noninfectious origin and the substantial systemic cytokine release unparalleled by the average COVID-19 patient (2). Given uncertain clinical benefits of agents that may exacerbate existing pandemic health inequities, multiple clinical trials are being conducted or have been completed, with the pendulum still in swing. In the BACC-BAY double-blind RCT, Stone et al (17) demonstrate that tocilizumab does not reduce time to intubation or death in patients with early COVID-19 not on mechanical ventilation (MV). In this trial, 96% of the patients were categories 2–3 on the seven-category ordinal-scale at baseline, and approximately 10% received glucocorticoids. EMPACTA, a double-blind RCT, included 377 patients hospitalized with COVID-19 not on non-invasive ventilation (NIV) or MV. As compared to standard of care, tocilizumab reduced the likelihood of the composite primary outcome of progression to MV or death, although it did not improve survival. In EMPACTA, 26.5% of the patients were in category 4 on the ordinal-scale at baseline, and approximately 83% of those enrolled received glucocorticoids (18). In a preprint of the COVACTA trial, a double-blind RCT, which included 438 critically ill patients, clinical status at day 28 was not statistically significantly improved for tocilizumab versus placebo. In this trial, 68% of the patients were greater than or equal to category 4 on the ordinal-scale at baseline, 37% were receiving MV, and approximately 42% of those enrolled received glucocorticoids. Although the median duration of ICU stay and time to hospital discharge was shorter in tocilizumab arm, there was no difference in 28 day mortality (35). Finally, in a press release followed by a preprint, REMAP-CAP investigators report that in their international, multifactorial, adaptive platform trial, among 865 critically ill patients on organ support (high flow nasal cannula, NIV, MV, or vasopressors), tocilizumab and sarilumab significantly improved the primary outcome of organ support free days at day 21 as well as significantly improving hospital survival. Eighty-three percent of the patients had received glucocorticoids. The sum of these trials emanates uncertainty about the clinical benefits and cost effectiveness of IL-6 inhibitors in COVID-19. Enter RECOVERY. The tocilizumab arm in the RECOVERY trial has closed at 4,100 patients, with follow-up ongoing.

TABLE 1.
Clinical Trials Exploring the Use of Cytokine Inhibitors in Sepsis and/or Acute Respiratory Distress Syndrome

| Year | References | Population Studied | Power | Study Design | Intervention | Outcome | Septic Shock 28 d Mortality in Control Group, % |
|------|--------------------------|---|-------|---|---|---|---|
| 1994 | Fisher et al (3) | Sepsis or septic shock | 99 | Multicenter, randomized, open-label, placebo-controlled trial | rhIL-1ra | Dose-dependent reduction in mortality | – |
| 1994 | Fisher et al (4) | Sepsis or septic shock | 893 | Multicenter, randomized, double-blind, placebo-controlled trial | rhIL-1ra | No reduction in mortality. Increase in survival time in patients with more severe disease | – |
| 1995 | Abraham et al (5) | Sepsis stratified into shock or nonshock groups | 971 | Multicenter, randomized, double-blind, placebo-controlled trial | TNF- α MAb | Trend toward reduction in mortality among those with shock | 27.5 |
| 1996 | Fisher et al (6) | Septic shock | 141 | Multicenter, randomized, double-blind, placebo-controlled trial | TNF- α receptor:Fc fusion protein | No reduction in mortality. Dose-related increase in mortality | 30 |
| 1996 | Cohen et al (7) | Sepsis stratified into shock or nonshock groups | 533 | Multicenter, prospective, placebo-controlled trial | TNF- α MAb | No reduction in mortality. More rapid reversal of shock in treatment arm | 42.9 |
| 1997 | Opal et al (8) | Severe sepsis or septic shock | 696 | Multicenter, randomized, double-blind, placebo-controlled trial | rhIL-1ra | No reduction in mortality. Terminated after an interim analysis. | – |
| 1997 | Abraham et al (9) | Severe sepsis stratified into severe sepsis or refractory shock | 498 | Multicenter, randomized, double-blind, placebo-controlled trial | Lenercept (TNF- α inhibitor) | No reduction in mortality. Trend toward reduced mortality in severe sepsis group. | – |
| 1998 | Abraham et al (10) | Septic shock | 1,879 | Multicenter, randomized, double-blind, placebo-controlled trial | TNF- α MAb | No reduction in mortality. | 42.8 |
| 2001 | Abraham et al (11) | Severe sepsis or early septic shock | 1,342 | Multicenter, randomized, double-blind, placebo-controlled trial | Lenercept (TNF- α inhibitor) | No reduction in mortality. No effect on incidence or resolution of organ dysfunctions. | 34 |
| 2010 | Rice et al (12) | Severe sepsis and shock or respiratory failure | 274 | Multicenter, randomized, double-blind, placebo-controlled trial | TAK-242 (TLR-4 inhibitor) | No reduction in mortality. Failed to suppress IL-6 levels. | – |
| 2013 | Opal et al (13) | Severe sepsis | 1,961 | Multicenter, randomized, double-blind, placebo-controlled trial | Eritoran (TLR-4 inhibitor) | No reduction in mortality. No effect on cytokine levels | 28 |
| 2013 | Joannes-Boyou et al (14) | Septic shock and acute kidney injury for < 24 hr | 140 | Multicenter, prospective, open-label, randomized controlled trial | High-volume hemofiltration (70 mL/kg/hr) vs standard volume hemofiltration (35 mL/kg/hr) for 96-hr period | No reduction in mortality. Similar time to improvement in vitals and organ function | 40.8 |

(Continued)

TABLE 1. (Continued).
Clinical Trials Exploring the Use of Cytokine Inhibitors in Sepsis and/or Acute Respiratory Distress Syndrome

| Year | References | Population Studied | Power | Study Design | Intervention | Outcome | Septic Shock 28 d Mortality in Control Group, % |
|------|---------------------------------|--|-------|---|--|---|---|
| 2017 | Schadler et al (15) | Mechanically ventilated patients with severe sepsis and septic shock and acute lung injury or acute respiratory distress syndrome | 100 | Multicenter, open-label, randomized controlled trial | Cytosorb hemoperfusion for 6 hr/d for up to 7 consecutive d | No difference in plasma IL-6 levels | – |
| 2020 | Salvarani et al (16) | COVID-19 pneumonia not on NIV or MV, with P_{aO_2}/F_{iO_2} 200–300 mm Hg and inflammatory phenotype: fever and elevated CRP | 126 | Multicenter, randomized, open-label, clinical trial | IV tocilizumab (8 mg/kg) every 12 hr for two doses | Interim analysis showed futility. No benefit in disease progression. No reduction in mortality. | – |
| 2020 | Stone et al (17) | COVID-19 pneumonia with fever, pulmonary infiltrates, or a need for oxygen < 10 L/min and CRP > 50 mg/L, or ferritin > 500 ng/mL, or D-dimer > 1,000 ng/mL, or lactate dehydrogenase > 250 U/L | 243 | Multicenter, randomized, double-blind, placebo-controlled trial | IV tocilizumab (8 mg/kg) × 1 | Not effective for preventing intubation or death in moderately ill COVID-19 patients | – |
| 2021 | Salama et al (18) | COVID-19 pneumonia not on NIV or MV with Sp_{O_2} < 94% on ambient air | 377 | Randomized, double-blind, placebo-controlled trial funded by Genentech | IV tocilizumab (8 mg/kg) for up to two doses | Reduced the likelihood of progression to the composite outcome of MV or death. No reduction in mortality. | – |
| 2020 | COVACTA Rosas et al Preprint | Critically ill COVID-19 pneumonia with Sp_{O_2} < 93% or P_{aO_2}/F_{iO_2} < 300 mm Hg | 438 | Global, multicenter, randomized, double-blind, placebo-controlled trial funded by | IV tocilizumab (8 mg/kg) | Tocilizumab did not improve clinical status at day 28. No reduction in mortality. | – |
| 2021 | REMAP-CAP Gordon et al Preprint | Critically ill suspected or confirmed COVID-19 pneumonia receiving organ support (high flow nasal canula, NIV, MV, or vasopressors) | 865 | International, multifactorial, adaptive platform trial | IV tocilizumab (8 mg/kg) for up to two doses; Sarilumab 400 mg × 1 | Tocilizumab and Sarilumab significantly improved the primary outcome of organ support free days at day 21. Significantly improved hospital survival | – |

COVID-19 = coronavirus disease 2019, CRP = C-reactive protein, IL = interleukin, MV = mechanical ventilation, NIV = noninvasive ventilation, rhIL-1ra = recombinant human IL-1 receptor antagonist, Sp_{O_2} = oxygen saturation, TLR = toll-like receptor, TNF- α Mab = TNF- α monoclonal antibody, TNF- α = tumor necrosis factor- α .

This table represents the key studies testing cytokine inhibition in critically ill patients suspected to have dysregulated cytokine cascade due to various infectious etiologies. Dashes indicate septic shock 28 day mortality is not available for the control group.

This lack of congruency in evidence with a shifting pendulum is not foreign to the field of critical care medicine with our history tainted with many such examples. Although we await peer review of COVACTA and REMAP-CAP trials, results of the RECOVERY trial, and a pooled analysis of IL-6 inhibitors in critically ill patients, caution is warranted in premature, indiscriminate adoption into clinical practice.

EVIDENCE BEHIND BLOOD PURIFICATION FOR CYTOKINE REMOVAL IN SEPSIS AND/OR ARDS

To date, anticytokine therapy has not succeeded in improving outcomes in patients with the “cytokine storm” of sepsis and/or ARDS. An alternative approach that has been put to test is extracorporeal blood purification to remove cytokines (36). With standard continuous renal replacement therapy, cytokines can be removed via both convective elimination and to a lesser degree adsorptive clearance depending on the filter characteristics. Hence, it has been postulated that high-dose continuous venovenous hemofiltration (CVVH) may potentiate cytokine clearance and improve outcomes in sepsis. However, a multinational RCT comparing high-volume CVVH (70 mL/kg/hr) with standard volume CVVH (35 mL/kg/hr) in patients with septic shock and acute kidney injury (AKI) did not demonstrate improvements in 28-day mortality, hemodynamic profile, or organ function (14). Given previous preliminary studies demonstrating that membrane adsorption, rather than convective elimination, may be the main clearance mechanism for cytokines, enhanced filter sets with heightened adsorptive properties emerged. Cytosorb is a novel whole blood adsorber with the ability to remove cytokines. A limited quality, open-label, multicenter, RCT with 100 patients with severe sepsis or septic shock and ARDS on MV failed to demonstrate a reduction in plasma IL-6 levels, with adjusted analysis showing no association with survival in the group undergoing Cytosorb hemoperfusion for 6 hours/d for up to 7 consecutive days (15). oXiris hemofilter (Baxter) is a high permeability polyacrylonitrile (AN69)-based membrane with a positively charged polyethylenimine surface treatment making it a membrane with one of the highest adsorption capacities for both endotoxins and cytokines (37). Animal studies

showed clinical benefit in septic pigs (38). There are limited data in humans demonstrating a reduction in cytokine levels and stabilization of hemodynamics in non-COVID septic or COVID-19 patients treated with the oXiris hemofilter (39–41). The inherent limitations of observational data calls for only cautious optimism and the jury is still out on the effectiveness of these sorbents in treating the consequences of the expected cytokine cascade following an infection.

LESSONS LEARNED, APPLICABILITY TO COVID-19 AND FUTURE DIRECTION

The COVID-19 pandemic, the largest since the Spanish flu, has threatened the survivability of evidence-based medicine (EBM). EBM is defined as the “conscientious, explicit, judicious and reasonable use of modern, best evidence in making decisions about the care of individual patients” (42). A principled approach to patient care integrates the best available evidence, clinical experience, and patient values to make critical decisions. During a pandemic, the idealistic progression of investigation from bench to bedside may not be timely available. With the speed and severity of the impact, the temptation to race ahead of the evidence and use therapeutics with theoretical sound reasoning, in the absence of robust trials, may be difficult to battle. However, the value of vigorously conducted RCTs, to inform physicians, patients, and families, remains paramount even during a pandemic. Here, we journey through the last 3 decades of discouraging data on cytokine inhibitors to tackle sepsis and/or ARDS—conditions with a more profound systemic release of cytokines than the so-called “cytokine storm” of severe and critical COVID-19 (2). We have learned, ad nauseam, that although cytokine inhibitor monotherapy in sepsis has theoretical plausibility, time and again, it has failed the test of a large controlled clinical trial.

Why May Anticytokine Therapy Fail In Sepsis and/or ARDS?

The complexity, heterogeneity, and built in redundancy of the host inflammatory response to pathogens cannot be underestimated. Despite an indistinguishable clinical presentation of “cytokine storms” of various etiologies, the inflammatory milieu and cytokine profile may be distinct from patient to patient (2).

It is impacted by the infecting pathogen, microbial load, and various host factors including genetic composition, age, comorbidity, and medications. Hence, a blanket approach of administering a specific cytokine inhibitor to all patients with infection-induced dysregulated immune response may be misguided. Furthermore, redundancies in the inflammatory signaling system make it difficult to obviate the consequences of the cytokine cascade by inhibiting a single cytokine. By paralyzing a single cytokine, we target a very small limb of a complex, redundant, interdependent, nonlinear, nonuniform downstream pathway. Finally, in animal models of peritoneal sepsis, it has been demonstrated that although fulminant sepsis results in significant IL-6 elevations, with levels predicting mortality, sepsis impairs the intracellular response to the circulating IL-6 (43). Andrejko et al (44) demonstrated that fulminant peritoneal sepsis in rats decreased the ability of hepatocytes to respond to IL-6. This loss of serum and intrahepatic IL-6 activity correlated with mortality. It has been proposed that this failed intracellular response to increased serum IL-6 levels in sepsis stimulates ongoing and enhanced IL-6 production, albeit it lacks efficacy at the cellular level, making it an unsuitable therapeutic target. This may partly explain why anticytokine therapy targeting the already “impotent” cytokines has failed to ease the septic response or improve survival. Traditional measurements cannot identify impaired or preserved intracellular responsiveness to circulating cytokines to differentiate whether circulating cytokines are pathologic or impotent. As such, among the septic cohort, it is possible that some have excessive inflammation, whereas others have insufficient inflammation to effectively eradicate the infectious source. Hence, existing clinical trials with indiscriminate recruitment of all septic patients may lack power to detect benefit, if any, of anticytokine therapy in the subgroup that in fact has preserved cytokine responsiveness. However, it is challenging to identify that cohort with the only measurable component in the signaling cascade being the cytokine itself.

Why May Blood Purification for Cytokine Removal Fail in Sepsis and/or ARDS?

The lack of success of various forms of extracorporeal blood purification, whether it be convective or adsorptive clearance, may be explained by the nonspecific

nature of this modality which does not discriminate between proinflammatory and anti-inflammatory mediators and eliminates both (45). Hence, the pro-/anti-inflammatory balance might remain unaffected. There is also little control over the degree of cytokine clearance; what is a good cytokine level? There are a few additional critical points to keep in consideration when using these treatments in the absence of AKI. Critically ill patients are usually on various concomitant medications. Depending on the filter used, these treatments may remove a portion of administered medications including antibiotics, decreasing their efficacy. Additionally, CVVH may remove certain biomarkers and give clinicians a false sense of security regarding the patients' clinical status. These removable biomarkers include C-reactive protein monomer, procalcitonin, and brain natriuretic peptide (46). Finally, CVVH, especially at higher doses can remove essential electrolytes mandating close monitoring and replacement.

Using Existing Literature to Guide Therapy in COVID-19

To date, anticytokine therapy has failed to serve a role in sepsis and/or ARDS. Whether it will find a place in the armamentarium against COVID-19 remains unknown. With notable debate, we do not yet have a decisive take on the immunopathology in COVID-19, with considerable heterogeneity from patient to patient. Two conflicting paradigms exist—one of an overexuberant immune response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with excessive proinflammatory cytokines and the other of immunologic collapse with unrestrained viral dissemination.

In alignment with the latter hypothesis, evidence suggests that although patients with COVID-19 have higher than normal median levels of circulating proinflammatory cytokines, with IL-6 levels predicting degree of severity and outcomes (47), as compared to non-COVID ARDS, sepsis, and CRS, the median systemic levels in severe and critical COVID-19 are trivial (2, 48–50). “Cytokine storm” is an unsuitable attribute. As an example, Leisman et al (2) demonstrated that as compared to COVID-19, mean IL-6 concentrations were nearly 100 times higher in patients with CRS, 27 times higher in patients with sepsis, and 12 times higher in patients with non-COVID ARDS. Whatever the levels of circulating IL-6 in COVID-19, whether

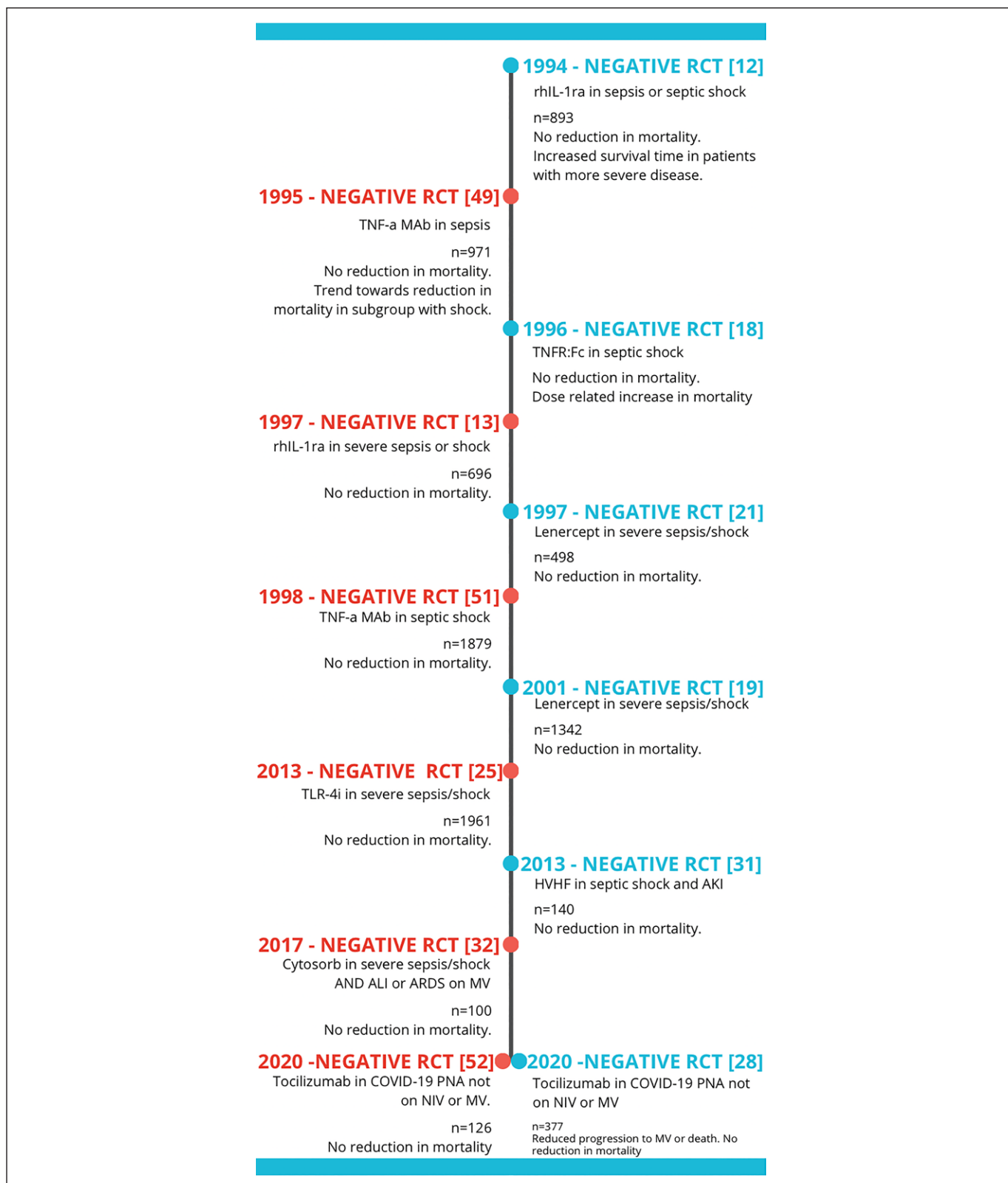


Figure 1. A timeline depicting key randomized controlled, peer reviewed trials of cytokine inhibition among critically ill patients suspected to have infection-induced dysregulated cytokine cascade. ALI = acute lung injury, ARDS = acute respiratory distress syndrome, COVID-19 = coronavirus disease 2019, HVHF = high-volume hemofiltration, MVMV = mechanical ventilation, NIV = noninvasive ventilation, PNA = pneumonia, RCT = randomized controlled trial, rhIL-1ra = recombinant human interleukin-1 receptor antagonist, TLR-4i = toll-like receptor-4 inhibitor, TNFR:fc = TNF- α receptor:Fc fusion protein, TNF- α Mab = TNF- α monoclonal antibody, TNF- α = tumor necrosis factor- α .

there is concomitant impairment in cytokine signal transduction at the cellular level, akin to sepsis, is not yet known. Although IL-6 is a reliable marker for disease severity and mortality in COVID-19, its contribution to pathogenesis remains unclear. Additionally, in the context of injury or infection, various types of epithelial cells including renal, pulmonary, and bronchial cells are capable of producing IL-6 (50, 51). Hence, in COVID-19, IL-6 elevations could indicate production from epithelial cells/cell injury with quantified levels suggesting severity, but not necessarily implying pathogenesis, again making it a poor target for treatment. Here, it is important to reiterate what sets CRS, a condition that responds to pharmacologic inhibition of IL-6, apart—the massive cytokine release and the lack of endotoxemia or sepsis—making the circulating IL-6 indisputably potent and pathogenic and hence an excellent therapeutic target. In an elegant study, Remy et al (50) further characterize the quantitative and qualitative peripheral immune defects in patients with COVID-19. T lymphocytes are directly susceptible to SARS-CoV-2 infection, and profound and progressive lymphopenia was a common feature in COVID-19 with nonsurvivors likely to have persistent lymphopenia. As compared to patients with sepsis, peripheral innate and adaptive immune cells (monocytes and T cells) from COVID-19 patients who experienced mortality within 30 days were phenotypically suppressed with only a proportion of cells producing TNF- α and interferon (IFN)- γ when challenged with *ex vivo* stimulation. Notably, there was heterogeneity, with nonsurvivors maintaining lower numbers of TNF- α and IFN- γ producing cells than survivors. In another study, using single-cell transcriptomics, it was demonstrated that peripheral monocytes, T cells, and natural killer cells in patients with COVID-19 did not have substantial expression of proinflammatory cytokine genes. The authors suggest that at least these cells do not contribute to the unsubstantiated “cytokine storm” in COVID-19 (51). If this paradigm of “immunologic collapse” prevails, it shakes the very foundations based on which the hypothesis of anticytokine therapy in COVID-19 thrives.

Conversely, in a study supporting immune-mediated organ injury, Dorward et al (52) characterize the tissue-specific immunopathology in patients with COVID-19. On postmortem examination, they detected SARS-CoV-2 RNA across all sampled organs

and tissue sites although there was considerable inter-patient variation in the tissue sites involved. Among the organs involved, lung and reticuloendothelial system were the exclusive sites of an extensive inflammatory response, whereas extrapulmonary sites with evidence of viral transcription did not have substantial local inflammation. The viral RNA involvement was patchy and had no topologic association with the lung inflammatory response. The authors suggest that this could be explained by either nonresolving inflammation after viral clearance or by inflammation in areas of the lung where viral replication had never occurred. It is important to define whether the inflammation has an antiviral role or is a hyperinflammatory response to the virus, each with different treatment implications. The latter explanation could be consistent with the beneficial effect of corticosteroids in severe disease. Similarly, patchy but striking myeloid related protein 8 mononuclear-cell vasculitis predominantly affecting intima of small/medium-sized pulmonary arteries was observed in some patients. These were accompanied by a mixed population of CD4⁺ and CD8⁺ T cells and macrophages. Although a small study, it motivates future studies to understand the immune microenvironment at the organ level.

The notable heterogeneity in the immune response to COVID-19 between individual patients makes recruitment into clinical trials a daunting task. With limited understanding of the peripheral and tissue-specific immune milieu of COVID-19, data on IL-6 inhibitors in patients with COVID-19 are inconsistent, to date. Both trials demonstrating encouraging results had greater than 50% of patients concomitantly receiving glucocorticoids (EMPACTA and REMAP-CAP). In both EMPACTA and REMAP-CAP, among those patients who received steroids, a greater benefit was observed with tocilizumab than with placebo with respect to the primary outcome. What sets the current decade apart from the previous decades and trials on cytokine inhibitors is the adoption of glucocorticoids into clinical practice for ARDS and sepsis. Whether IL-6 inhibitors provide adjunctive benefit when combined with the broader inhibitory effects of glucocorticoids shall become clearer as more data emerge. Tocilizumab continues to be evaluated in the RECOVERY trial (NCT04381936) which should help further our understanding on the therapeutic implications of cytokine inhibitors in COVID-19.

CONCLUSIONS

The grim history of anticytokine therapy in critically ill patients with infection-induced cytokine cascade breeds therapeutic humility. Without a clear understanding of the immune response to COVID-19, any hypothesis promoting immunotherapy may be foundationally mistaken and distracting. Perhaps, the best therapy for patients in a pandemic is clenching on to the mantra of “less is more” by optimizing standard of care with parallel enrollment into scientifically sound clinical trials. As per the wisdom of Sir William Osler, “The person who takes medicine must recover twice. Once from the disease and once from the medicine.”

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The publication of this article was funded by the Weill Cornell Medicine - Qatar Distributed eLibrary.

The authors have disclosed that they do not have any potential conflicts of interest.

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