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MINI REVIEW

The cytokine storm of severe influenza and development of immunomodulatory therapy

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Severe influenza remains unusual in its virulence for humans. Complications or ultimately death arising from these infections are often associated with hyperinduction of proinflammatory cytokine production, which is also known as 'cytokine storm'. For this disease, it has been proposed that immunomodulatory therapy may improve the outcome, with or without the combination of antiviral agents. Here, we review the current literature on how various effectors of the immune system initiate the cytokine storm and exacerbate pathological damage in hosts. We also review some of the current immunomodulatory strategies for the treatment of cytokine storms in severe influenza, including corticosteroids, peroxisome proliferator-activated receptor agonists, sphingosine-1-phosphate receptor 1 agonists, cyclooxygenase-2 inhibitors, antioxidants, anti-tumour-necrosis factor therapy, intravenous immunoglobulin therapy, statins, arbidol, herbs, and other potential therapeutic strategies.
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1. INTRODUCTION

Newly emerging and re-emerging viral threats have continued to challenge medical and public health systems and incur economic costs to both individuals and countries. The influenza virus is a main cause of those threats and is responsible for millions of severe cases and 250 000–500 000 deaths each year.[1] The scenario can be even worse during a pandemic year. The most virulent influenza, the 1918 H1N1 Spanish flu, infected approximately 5% of the world's population and killed 2%.[2] The case fatality rates for the 1957 H2N2 Asian influenza, the 1968 H3N2 Hong Kong influenza, and the 2009 H1N1 pandemic influenza were reported to be lower, with an estimated rate of 0.2% or less.[3] Most alarmingly, between 1997 and 2014, several unprecedented epizootic avian influenza viruses (e.g., H5N1, H7N9, and H10N8) crossed the species barrier to cause human death. They pose an increasing threat of human-to-human transmission.[4,5] These infections in humans are accompanied by an aggressive pro-inflammatory response and insufficient control of an anti-inflammatory response, a combination of events called 'cytokine storm'.

In the event of influenza infection, the severity of disease is the result of the interplay between viral virulence and host resistance. In mild infection, the host has a limited or moderate resistance, so the disrupted homeostasis is restored rapidly. However, for infections caused by the 1918 H1N1 or the H5N1 influenzas virus, the resistance became hyperactive, resulting in an excessive inflammatory reaction known as the cytokine storm phenomenon.[6] Several experimental studies and clinical trials suggested that cytokine storm correlated directly with tissue injury and an unfavorable prognosis of severe influenza.[7] However, our understanding of the mechanism that promotes a cytokine storm remains limited. In this review, we focus on the potential mechanisms responsible for severe influenza-induced cytokine storm and the therapeutic strategies that might be used to improve the clinical prognosis of these infections.

2. THE PATHOLOGY OF CYTOKINE STORM

Respiratory epithelial cells, the primary targets for influenza virus, are also the choreographers of cytokine amplification during infection.[8] Following primary exposure, progeny

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viruses that proliferate within these cells can infect other cells, including alveolar macrophages.[9] Inflammatory responses are triggered when infected cells die by apoptosis or necrosis.[3] The initial response of the organism to harmful stimuli is acute inflammation and is characterized by increasing blood flow, which enables plasma and leukocytes to reach extra-vascular sites of injury, elevating local temperatures, and causing pain.[3] The acute inflammatory response is also marked by the activation of pro-inflammatory cytokines or chemokines.[9,10] These pro-inflammatory cytokines or chemokines can lead to the recruitment of inflammatory cells.[9,10] Then, an increasing expression of inflammatory, antiviral, and apoptotic genes occurs accompanied by abundant immune cell infiltration and tissue damage[7,11] (Figure 1). At the same time, regenerative processes and resolution of the damage are initiated. In most cases, function can be completely restored by this reparative process.[12] However, for severe inflammation associated with cytokine storm, more serious pathological changes are observed, such as diffuse alveolar damage, hyaline membrane formation, fibrin exudates, and fibrotic healing.[10] These are signs of severe capillary damage, immunopathologic injury, and persistent organ dysfunction.[10] Moreover, the severe inflammatory cytokines/chemokines can spill over into the circulation and result in systemic cytokine storms, which are responsible for multi-organ dysfunction.[7]

The inflammatory response begins when the pathogen-associated molecular pattern (PAMP) from the virus is recognized by the pattern recognition receptors (PRRs) of innate immune cells.[13,14] Then, specific pro-inflammatory cytokines are expressed after the downstream signaling cascades of PRRs are triggered by

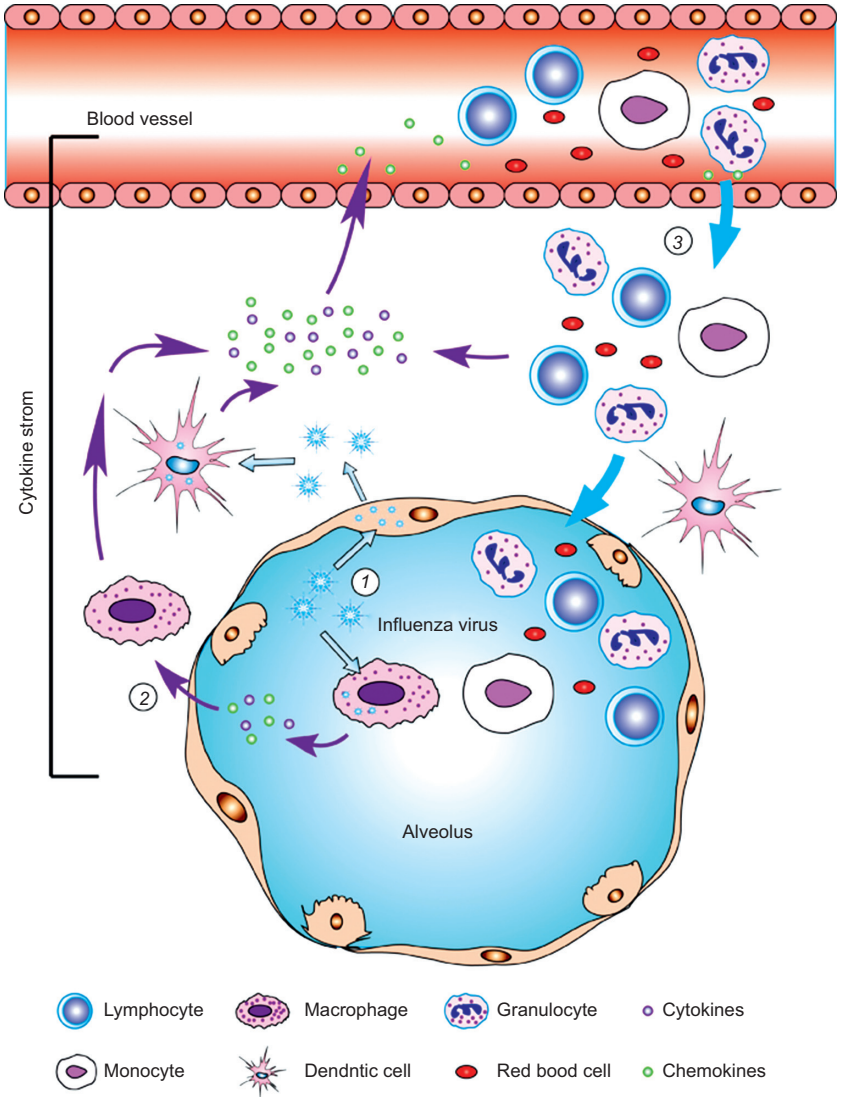

Figure 1 Cytokine storm in the lung following severe influenza infection. (1) Viruses infect lung epithelial cells and alveolar macrophages to produce progeny viruses and release cytokines/chemokines (mainly contains interferons). (2) Cytokine/chemokine-activated macrophages and virally infected dendritic cells lead to a more extensive immune response and the initiation of cytokine storm. (3) Released chemokines attract more inflammatory cells to migrate from blood vessels into the site of inflammation, and these cells release additional chemokines/cytokines to amplify cytokine storm.

stimuli.[14] Researchers have a great interest in exploring the association between polymorphisms of PRRs and host susceptibility to cytokine storm, which may help explain why some individuals, but not others, seem relatively resistant to cytokine storm.[15]

Severe cytokine storm, with markedly higher levels of pro-inflammatory cytokines including interferons (IFNs), tumor necrosis factors (TNFs), interleukins (ILs), and chemokines, has been detected in patients hospitalized with severe influenza infections.[16] Severe cytokine storm is rarely observed in seasonal and other mild influenza,[17] indicating that high cytokine/chemokine levels correlate strongly with disease severity. The interferon family has a critical role in the innate immune response to viruses.[18] A number of proteins with antiviral or immunomodulatory properties are produced once the IFN signaling pathway is activated.[18] Although overproduction of IFN in the early stage of infection likely leads to irreversible lung damage in H5N1-infected mice, the IFN signaling pathway may also be important in restricting the dissemination of H5N1 viruses.[18,19] TNF-α is a key cytokine in cytokine storm and is likely to account for the escalation in severity.[12] However, TNF receptor$^{-/-}$ mice, or mice treated with anti-TNF-antibodies, have no changes in survival when compared with controls following a challenge with the H5N1 virus.[12] IL-1 and IL-6 are the main pro-inflammatory cytokines released by hosts during viral infections. IL-1 is expressed in the early stages of infection, followed by an increasing expression of IL-6.[7] IL-1 receptor signaling is responsible for acute the immunopathology of tissue, and IL-1 receptor$^{-/-}$ mice were shown to have a worse outcome after H5N1 infection. This suggests that the pathways are protective.[7]

Unlike pro-inflammatory cytokines, chemokines often have specific chemotactic activities that enable monocytes and T-lymphocytes to migrate from blood vessels into the site of inflammation.[9] For example, IL-8 and monocyte chemoattractant protein (MCP)-1 are major chemotactic factors for neutrophils and monocytes, respectively. It should be noted that the levels of IL-8, interferon-induced protein (IP)-10, MCP-1, macrophage inflammatory protein (MIP)-1, and monokines induced by IFN-γ (MIG) were abnormally elevated in some fatal cases of H5N1 influenza infection and that IL-8 had the highest level among them.[20] MIP-1$^{-/-}$ mice exhibit inefficient viral clearance but reduced mortality and lung damage.[9] Several studies[9,21] also investigated the roles of several chemokine receptors, such as the MIP-1 receptor CCR5 and the MCP-1 primary receptor CCR2, in severe influenza infections. Interestingly, CCR5$^{-/-}$ mice displayed an excessive inflammatory response and increased mortality, while CCR2$^{-/-}$ mice displayed a decreased inflammatory response and mortality but developed a significantly elevated viral load.[21] This evidence partly suggests that the pathology of severe influenza is mediated by cytokine response but not viral load.

Generally, the cytokine response induced directly by the influenza virus is a sprawling network, which is amplified by autocrine and paracrine mediator cascades. Pathways associated with PRRs, ILs, IFNs, TNFs, cyclooxygenase (COX)-2, and c-Jun N-terminal kinase (JNK) are activated to induce the transcription of NF-kB and the formation of inflammasomes.[7] A cytokine/chemokine-driven feed-forward inflammatory circuit may be responsible for the escalation of cytokine storm.[22] However, the key factors of this network, especially those specific to the pathogenesis of severe influenza, are still unknown. By using network-based systems biology approaches, Jin *et al.*[22] have made a successful attempt in elucidating the network properties of severe influenza. Their study demonstrated that TLR2, IL-1β, IL-10, and nuclear factor-kappa B have obvious differences between the normal and inflammatory networks.[22]

Complications arising from severe influenza are associated with inflammatory cells. Monocytes/macrophages are the main cells recruited into the alveolar space as an initial response to viral infection.[3,9] They then increase their cytokine production and chemoattract additional immune cells into the lesion area.[3,9] Nevertheless, they are also susceptible to influenza viral infection. Depleting the monocytes/macrophages does not prevent immunopathology, indicating their important role in viral clearance.[3,9]

Both CD4 and CD8 T cells are responsible for the immunopathology and viral clearance of infection. A lethal lung injury can be triggered by the transfer of antigen-specific CD8 T cells into transgenic mice expressing the influenza HA antigen. However, a lethal lung injury cannot be triggered in mice with defects in the epithelial early growth response-1 (Egr-1), suggesting that Egr-1 is a critical regulator of the immunopathology of CD8 T cells.[23] CD4 T cells (including Th1, Th2, Th17, and Treg) have been identified to contribute to both immunopathology and viral clearance of influenza infection. Severe respiratory disease of influenza is often characterized by the early secretion of Th1 and Th17 cytokines.[24] Tregs (regulatory CD4$^{(+)}$Foxp3$^{(+)}$ T cells) are key managers in controlling the degree of cellular immune responses to viral infections. Particularly, the proliferation of memory CD8(+) cells can be effectively controlled by the memory Tregs in an Ag-specific manner that is MHC class II dependent.[25]

3. IMMUNOMODULATORY THERAPY

As the outcome of severe influenza is determined by both viral virulence and host resistance, the use of immunomodulatory therapy in combination with conventional antiviral therapy is highly warranted. In fact, several studies have confirmed that the mortality and organ injury of severe influenza can be reduced by immunomodulatory agents, with or without the combination of antivirals. Moreover, many of them are relatively inexpensive and easily produced drugs, which could potentially be widely used in an influenza pandemic. Here, we review the properties of these agents (Table 1).

3.1. Corticosteroids

Corticosteroids are a class of steroid hormones that exhibit anti-inflammatory activity via binding to the cytoplasmic corticosteroid receptor, which regulates transcription of anti-inflammatory genes.[26] Thus, corticosteroids have been widely

used for anti-inflammatory treatment. During the 2009 H1N1 influenza pandemic, nearly 40% of patients in France were treated for acute respiratory distress syndrome (ARDS) using adjuvant systemic corticosteroids.[27] During the 2013 H7N9 avian influenza outbreak in China, 62.2% of patients received systemic corticosteroid treatment.[28] However, the evidence supporting the use of corticosteroids in severe influenza is inconclusive. An experimental study has shown that mice infected with H5N1 influenza have a similar mortality between the corticosteroid-treated group and the control group.[29] A clinical trial even identified that systemic corticosteroids were responsible for an increased long-term mortality.[27] In contrast, another independent research study reported that systemic use of corticosteroids alleviated the 2009 H1N1 pandemic influenza-associated pneumonia without adverse outcomes.[30] Thus, the use of corticosteroids for severe influenza is controversial and still needs further observations.

3.2. Peroxisome proliferator-activated receptor agonists

Peroxisome proliferator-activated receptors (PPARs), including PPAR-α, PPAR-β, and PPAR-γ, are critical regulators of inflammation. The PPAR-α agonist, gemfibrozil, has been proposed to treat severe influenza due to ability to inhibit TNF, IL-6, and IFN-γ.[31] However, another research study[32] reported that gemfibrozil administered 48-h post-infection had no effects on the mortality of H5N1 avian influenza-infected mice. This suggests that the pharmacological mechanism of gemfibrozil to treat severe influenza still needs further characterization. There is little research on the use of PPAR-β agonists to treat severe influenza, perhaps focusing on their trophic effects on oligodendrocytes *in vitro*. Only bezafibrate was shown to have partial protection in patients with influenza-associated encephalopathy.[33] However, PPAR-γ agonists (e.g., rosiglitazone and pioglitazone) are considered to be the most promising candidates to improve the clinical outcome of severe influenza.[26] These thiazolidinediones can not only downregulate the inflammatory response to viral pneumonia but also increase the survival of influenza-infected mice.[34] Moreover, the benefits of PPAR-γ agonist treatment were found to be higher than gemfibrozil.[26] In addition, a natural PPAR-α and PPAR-γ agonist, biochanin A, which is extracted from red clover, has been confirmed to have similar immunomodulatory effects as gemfibrozil for the treatment of influenza *in vivo*.[35]

3.3. Sphingosine-1-phosphate receptor 1 agonists

In recent years, there has been an increasing interest in developing novel agents with anti-immunopathologic injury activity through the sphingosine-1-phosphate (S1P) receptor pathway.[36] Five specific S1P receptors have been found to regulate downstream signaling pathways. However, only S1P1, which is located mainly on pulmonary endothelial cells, exhibits cytokine-storm-blunting activity by suppressing both innate cellular and cytokine/chemokine responses.[36] For example, CYM-5442 and RP-002 have been reported to protect mice from lethal infection with severe influenza by blunting cytokines and innate immune cell recruitment.[8] Particularly, in murine models infected with the 2009 H1N1 pandemic influenza, S1P1 receptor agonists alone reduced over 80% of deaths from lethal infection compared to 50% protection offered by the antiviral neuraminidase inhibitor, oseltamivir.[36] Furthermore, a combined therapy with the two agents can achieve an optimal protection of 96%.[36] This is by far the most promising result in improving the outcome of severe influenza using an immunomodulatory strategy.

3.4. COX inhibitors

Selective COX inhibitors, such as celecoxib and mesalazine, have been widely used in clinics for their antipyretic, analgesic, and anti-inflammatory properties. The monotherapy of celecoxib in a murine model of influenza does not considerably modulate disease severity.[37] However, the use of COX-2 inhibitors in combination with neuraminidase inhibitors has been shown to improve the survival of mice infected with H5N1 influenza.[32] A triple combination therapy of zalamivir, celecoxib, and mesalazine significantly reduced the mortality and levels of cytokines/chemokines of infected mice.[32] These data demonstrate that COX-2 inhibitors may provide additional benefits when combined with antivirals.

3.5. Antioxidants

As reactive oxygen species (ROS) play a central role in inflammatory responses and viral replication, antioxidants that exert antiviral and anti-inflammatory effects may also be effective for the treatment of cytokine storm induced by severe influenza.[38] N-acetylcysteine (NAC), a modified form of the amino acid cysteine, was shown to inhibit both H5N1 replication and H5N1-induced production of pro-inflammatory molecules (e.g., IL6, CCL5, CXCL8, and CXCL10) in lung epithelial cells.[39] Glycyrrhizin, an inhibitor of hydroxysteroid dehydrogenase, was shown to inhibit H5N1 replication and pro-inflammatory gene expression.[40] Interestingly, an investigation showed that vitamin C was beneficial for patients suffering from severe avian influenza.[41] In fact, many plant-derived antioxidants (e.g., polyphenol, flavonoids, etc.) could also reduce the damage of epithelial cells and the mortality of mice caused by lethal influenza.[42–44] However, current evidence indicates that monotherapy using antioxidants had a limited effect on cytokine storm, and a combination with antivirals would still be needed.[45]

3.6. Anti-TNF therapy

Although we still do not fully understand the complex nature of cytokine storm, TNF is considered to be a key cytokine for acute viral diseases (e.g., influenza virus, dengue virus, and Ebola virus).[7] Indeed, experimental studies have shown that TNF not only affects the balance of the local microenvironment, but it also exerts broad systemic effects after entering into the circulation.[46] Thus, anti-TNF strategies may be a reasonable way to treat severe influenza. Studies have reported that treatments using TNF-neutralizing monoclonal antibodies or soluble TNF receptor fusion proteins can reduce the cytokine production and inflammatory cell infiltrates in influenza-infected murine lungs.[47,48] However, no improved survival

Table 1 Summary of immunomodulatory therapy or strategies against severe influenza

Therapeutic agents or strategies	Summary
Corticosteroids	Alleviated the 2009 pandemic H1N1 influenza-infected patients with pneumonia.[30] Ineffective as monotherapy in H5N1 influenza-infected mice.[29] Increased long-term mortality in influenza-infected patients with pneumonia.[27]
PPARs agonists	Ciglitazone and troglitazone decreased the mortality of influenza-infected mice.[34] Bezafibrate partially protected patients with influenza-associated encephalopathy.[33] Gemfibrozil also decreased the production of IL-1, IL-6, and IFN-γ, but has no effects on the mortality of H5N1-infected mice when administered 48-h post-infection.[31,32]
S1P1 receptor 1 agonists	Reduced mortality of 2009 pandemic H1N1 influenza-infected mice over 80%, compared with 50% protection of oseltamivir.[36]
COX inhibitors	Ineffective as monotherapy in H5N1 influenza-infected mice, while effective when in combination with neuraminidase inhibitors.[32]
Antioxidants	N-acetylcysteine and glycyrrhizin inhibited H5N1 replication and pro-inflammatory gene expression *in vitro*[39,40] but ineffective as monotherapy *in vivo*.[45]
Anti-TNF therapy	Effective in reducing the cytokine production and inflammatory cell infiltrates in influenza-infected murine lung but ineffective in improving survival of infected mice.[47,48]
IVIG therapy	Reduced 26% to 50% mortality of 2009 pandemic H1N1 and 1918 Spanish H1N1 influenza-infected patients.[50,52]
ACEIs or ARBs	Combined with caffeine or antivirals, alleviated lung injury and inhibited viral replication in H1N1, H3N2, and H5N1 influenza-infected mice.[54] Ineffective in protecting 2009 pandemic H1N1-infected patients.[55]
CCR inhibitor	Increased survival of influenza-infected mice by 75%.[58]
AMPK activators	Increased survival for influenza-infected mice by 40%, while a combination with pioglitazone improved survival by 60%.[59]
OX40	Imparted a survival signal to the T cell via upregulating anti-apoptosis gene expression and eliminated weight loss in influenza-infected mice.[60]
SOCSs	Participated in a negative feedback loop in the JAK and epidermal growth factor receptor pathway to protect against severe cytokine storm during severe influenza.[61]
Macrolide	Decreased mortality, pro-inflammation, and inflammatory cell counts of influenza-infected mice.[62]
Arbidol	Reduced the mortality, lung lesion formation, and inflammation of severe influenza-infected mice.[64]
Herbs	Favorable in laboratorial data but limited clinical data for severe influenza.[65–71]

rates were observed in these studies.[47,48] Thus, the evidence for the clinical use of anti-TNF therapy in severe influenza is currently inconsistent. Further clinical trials to evaluate the efficacy of anti-TNF strategies are still needed.

3.7. Intravenous immunoglobulin therapy

Intravenous immunoglobulin (IVIG) therapy uses concentrated globulin preparations from pooled human plasma for the treatment of acute infections. The mechanism by which IVIG suppresses harmful inflammation has not been definitively identified. It is believed to involve multiple immunomodulatory effects by blocking Fc receptors, which are associated with tolerance to self and severity of the inflammatory state.[49] This strategy has been used in the treatment of viral-induced cytokine storm and was confirmed to have improved the outcome in infections, such as SARS and the 2009 H1N1 pandemic influenza.[50,51] A meta-analysis suggested that early administration of blood products could have reduced anywhere from 26% to 50% of patients' deaths from pneumonia during the 1918 H1N1 influenza pandemic.[52] Evidence of a beneficial effect of IVIG therapy has been obtained in the 2009 H1N1 influenza infections. A multivariate analysis of the 22 patients who received either hyperimmune or normal IVIG within five days of symptom onset found that hyperimmune IVIG treatment was independently responsible for the reduced mortality of infection.[50] These results suggested that passive immunotherapy with hyperimmune globulin is a potential strategy for the treatment of severe influenza.

3.8. Other agents

Some inexpensive generics, such as statins, angiotensin receptor blockers (ARBs), and angiotensin-converting enzyme inhibitors (ACEIs), were also proposed as potential immunomodulatory agents to reduce inflammation caused by the influenza virus.[53] Statins are competitive inhibitors of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. They exert multiple immunomodulatory effects, such as (i) modulating the activation of immune effector cells via inhibition of ROS, (ii) antagonizing high mobility group box 1 protein (HMGB1) to inhibit pro-inflammatory cytokine expression, and (iii) suppressing CCR2 gene expression.[53] In murine models infected with H1N1, H3N2, or H5N1 influenza virus, the combination of statins and caffeine alleviated the lung injury, inhibited viral replication, and appeared to have similar efficacy as oseltamivir or ribavirin.[54] However, an independent research study showed that statins cannot prevent patients infected with the 2009 H1N1 pandemic influenza from developing severe disease.[55] No direct evidence was shown that ACEIs or ARBs might be effective in the therapy of severe influenza-induced cytokine storm. However, these agents can inhibit the inflammatory response induced by angiotensin II and improve the survival of mice in several experimental models of acute lung injury.[56] Furthermore, clinical trials also confirmed that these agents can reduce the risk of pneumonia and pneumonia-related mortality.[57] Thus, both the pharmacodynamic effects and mechanisms of these generics deserve further research.

Several other immunomodulatory agents are being assessed for their efficacy, both *in vitro* and *in vivo*. Lin and colleagues[58] have confirmed that CCR inhibitor-treated mice had a significant increase in survival (75% versus placebo) after being infected with influenza. Adenosine 5′-monophosphate-activated protein kinase (AMPK) is an enzyme that exerts anti-inflammatory effects after activation. The AMPK activator aminoimidazole carboxamide ribonucleotide (AICAR) was reported to increase survival by 40% in influenza-infected mice, while combination with pioglitazone improved survival by 60%.[59] OX40 (CD134) could impart a survival signal to T cells by upregulating anti-apoptosis gene expression, which plays a critical role in T-cell-mediated immunopathology in the lung during viral infection.[60] The OX40–immunoglobulin fusion protein (OX40–Igs) treatment was shown to block the interaction of OX40 with its ligand on antigen-presenting cells and eliminate weight loss and cachexia without preventing viral clearance in influenza-infected murine models.[60] It should be noted that some inhibitors of interferon γ signaling, such as suppressors of cytokine signaling (SOCSs), were shown to have negative regulatory properties and participated in a negative feedback loop in the JAK and epidermal growth factor receptor tyrosine kinase pathways.[61] These proteins are also potential agents that protect against cytokine storm during severe influenza.[61] All these findings offer a great deal of encouragement for treating influenza-induced cytokine storm with immunomodulatory agents.

Some antibiotics and antivirals are also known to possess anti-inflammatory effects and immunomodulatory properties in addition to their anti-pathogenic actions. Both *in vitro* and *in vivo* studies have provided ample evidence for the immunomodulatory and anti-inflammatory activity of macrolides (e.g., erythromycin, clarithromycin, roxithromycin, and azithromycin).[62] Macrolides can interfere with the replication cycle of influenza virus, resulting in the inhibition of viral production from infected cells. Moreover, macrolide treatment of influenza virus-infected mice increased survival, suppressed inflammation, and reduced inflammatory cell counts.[62] Arbidol is an antiviral that has complicated mechanisms. Both membrane-fusion-inhibition and immunomodulatory activity may contribute to its effects.[63] Our current research confirmed that post-treatment with arbidol-reduced mortality, lung lesion formation, and viral-induced inflammation by modulating the expression of pro-inflammatory cytokines in influenza-infected mice.[64] These data suggest that arbidol might also be effective in the treatment of severe influenza infections in humans.

Herbs may also be a potential choice for patients hospitalized with severe influenza. Several Chinese herbal prescriptions were recommended and authorized by the Chinese government during the 2009 H1N1 and 2013 H7N9 pandemics.[65,66] Systematic reviews for clinical trials of these herbs used in influenza treatment have revealed that few herbal medicines showed a positive effect on viral shedding, but they had a positive effect on resolution or relief of symptoms.[67,68] Moreover, many herbs exhibit beneficial immunomodulatory effects for the rapid recovery of viral infections and might be effective treatments for infection with severe influenza.[69] We have reported that extracts from Jiawei-Yupingfeng-Tang (a traditional Chinese herbal formula) can alleviate influenza-induced lung lesions with both antiviral and immunomodulatory activity.[70] We also have confirmed that epigallocatechin gallate (EGCG), a green tea-derived polyphenol, can inhibit the pathogenesis of influenza-infected cells due to its antioxidant activity.[71] Polyphenols, triterpenoids, and flavonoids, all from herbs, may potentially be active components in protecting against cytokine storm during severe influenza (unpublished data). However, confirmation in a larger series of clinical studies is required.

4. CONCLUSIONS

The persistent outbreaks of avian influenza in Asia and parts of Africa suggest that severe influenza, such as avian influenza, poses a major threat to public health. Many severe-influenza-infected patients died from overwhelming viral pneumonia and serious complications caused by cytokine storm. In this review, we have highlighted the pathology of cytokine storm and, in particular, how an enhanced broad immune response can sometimes worsen the outcome of disease. Although the precise molecular events surrounding cytokine storm have not been clarified, immunomodulatory strategies and novel approaches in targeting the host's response to severe influenza have been advocated. Considering that these agents work on different intracellular pathways, they might ideally be used in combination to obtain a better outcome. Based on the promising results mentioned above, combination therapies pairing S1PR and PPAR agonists, COX-2 inhibitors, and antioxidants with conventional antiviral agents are promising treatments that deserve further study in randomized clinical trials. Other approaches, especially those therapeutic strategies that can target signaling pathways, either to suppress redundant immune responses or reduce viral replication, will be particularly noteworthy.

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