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Review article

Preventing the development of severe COVID-19 by modifying immunothrombosis

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ABSTRACT

Background: COVID-19-associated acute respiratory distress syndrome (ARDS) is associated with significant morbidity and high levels of mortality. This paper describes the processes involved in the pathophysiology of COVID-19 from the initial infection and subsequent destruction of type II alveolar epithelial cells by SARS-CoV-2 and culminating in the development of ARDS.

Main body: The activation of alveolar cells and alveolar macrophages leads to the release of large quantities of proinflammatory cytokines and chemokines and their translocation into the pulmonary vasculature. The presence of these inflammatory mediators in the vascular compartment leads to the activation of vascular endothelial cells platelets and neutrophils and the subsequent formation of platelet neutrophil complexes. These complexes in concert with activated endothelial cells interact to create a state of immunothrombosis. The consequence of immunothrombosis include hypercoagulation, accelerating inflammation, fibrin deposition, migration of neutrophil extracellular traps (NETs) producing neutrophils into the alveolar apace, activation of the NLRP3 inflammazome, increased alveolar macrophage destruction and massive tissue damage by pyroptosis and necroptosis Therapeutic combinations aimed at ameliorating immunothrombosis and preventing the development of severe COVID-19 are discussed in detail.

1. Background

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has been classified as a zoonotic β-coronavirus which has entered the human population from an unknown animal host in a similar manner to the closely related SARS-CoV [1,2]. This virus is the cause of COVID-19. This is an illness which for the most part is associated with mild symptoms [3]. However, the illness may progress to severe pneumonia and acute respiratory distress syndrome (ARDS), leading to high levels of morbidity and mortality. Currently, the weight of evidence suggests that approximately 20% of patients infected with SARS-CoV-2 progress to severe disease requiring hospitalisation. Of those individuals admitted 20% develop pneumonia and ARDS with the latter group of patients requiring protracted ventilation [4,5]. Sadly, several authors

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have reported that the death rate in mechanically ventilated patients approaches 50% [4,5].

2. Immune, structural, physiological and biochemical abnormalities reported in COVID-19 ARDS

COVID-19 ARDS is exemplified by the existence of diffuse alveolar damage, increased epithelial and endothelial cell permeability, fibrin-rich hyaline membranes, leakage of fluid into the pulmonary interstitium and significant disruption of gas exchange, ultimately leading to the development of hypoxia and, in many cases, respiratory failure [4,6–8] reviewed in Ranucci et al. [9]. These features are typical findings in patients with ARDS secondary to sepsis or severe viral infections in these respects COVID-19 ARDS is unremarkable [10].

However there is evidence to suggest that there may be greater levels of coagulation cascade activation and greater decreases in the activities of the anticoagulant and fibrinolytic system in patients suffering from COVID-19 ARDS compared to those with ARDS secondary to other conditions or illnesses [9,11–13]. The relative importance of excessive hypercoagulation in the pathogenesis of severe COVID-19 is further highlighted by recent evidence which suggests that 70% of individuals who died as a result of SARS-CoV-2 infection satisfied the diagnostic criteria for disseminated intravascular coagulation (DIC), while that was only the case in 1% of survivors [14]. There is also extensive evidence of vascular endothelial cell activation and damage in patients with severe COVID-19 [15–17]. In addition it would appear that one source of such activation and damage is via direct infection by SARS-CoV-2 [17].

Several authors have reported the existence of significant levels of immune dysregulation in the lungs of patients with severe COVID-19 pneumonia or ARDS. For example, there is copious evidence of activated alveolar macrophages [6,18–20]. In addition, the absolute numbers these immune cells are depleted due to excessive levels of pyroptotic programmed death [18,21,22]. Other research teams have reported massively increased levels of activated neutrophils in lung interstitial tissue I and alveoli [7,23] review [24]. These neutrophils also appear to secrete significant levels of highly cytotoxic neutrophil extracellular traps (NETs) [7,25]. High levels of tumour necrosis factor (TNF) and influx of interleukin (IL)-1 secreting bone marrow derived monocytes of peripheral origin is also a common finding in these patients [26]. From a biochemical perspective it is interesting to note that these monocytes also secrete high levels of lactate dehydrogenase which is an accepted marker of immune cells undergoing death by pyroptosis [26]. The presence of hypercytokinemia in the lungs [18,27,28] and in the periphery [18,24,29–32] of patients with severe COVID-19 is another replicated finding. The pattern and intensity of cytokine and chemokine abnormalities is characteristic of cytokine release syndrome and a “cytokine storm” and many authors have suggested that this illness may be viewed as a virally induced sepsis [24,27,29,33–35].

To date the pathophysiology of COVID-19 ARDS has not been proposed and treatment options are limited. Accordingly, this paper proposes a model of the illness based on the observations cited above and extensive research into ARDS secondary to sepsis and or severe viral infections and discusses potential treatments targeting the proposed drivers of pathology.

3. The pathophysiology of COVID-19 ARDS

There is accumulating evidence that SARS-CoV-2 infects and activates type 2 alveolar epithelial cells resulting in the development of endoplasmic reticulum stress, NLP3 inflammasome activation and in many cases the death of these cells by apoptosis and pyroptosis [7,8,19,22,23,36,37]. Moreover, the weight of evidence suggests that SARS-CoV-2 may also infect and activate alveolar macrophages (AM). SARS-CoV-2 induced pyroptosis of type II alveolar cells may be a deterministic event in the development of COVID-19 ARDS as there is a growing body of evidence establishing a causative association between the initial pyroptosis of alveolar epithelial and endothelial cells and the ultimate development and progression of ARDS from other causes [38–40]. This association is due in part to the release of high mobility group box 1 (HMBG1) and other inflammatory DAMPS directly contributing to an escalating pattern of tissue damage [38–40].

The activation of AMs leads to their polarisation into a proinflammatory “M1” phenotype secreting high levels of proinflammatory cytokines (PICs) and chemokines such as TNF-alpha IL-1 beta, IL-6, and IL-8 [41–43]. Crucially, the subsequent release of these inflammatory mediators into the pulmonary vasculature plays an indispensable role in the development of ARDS by initiating a series of events which results in the activation of vascular endothelial cells [44–46], platelets [47–49], neutrophils [50,51], ultimately resulting in the formation of platelet neutrophil complexes at the surface of the endothelium [52–54]. The formation of these complexes encourages and enables the recruitment of highly cytotoxic neutrophils and inflammatory activated platelets into the alveolar space and pulmonary intestinal resulting in a host of pathogenic consequences, as discussed below [44–46].

One such consequence is the development of a highly inflammatory and pro-coagulant state typified by hyperactivation of the coagulation cascade and relative exhaustion of the fibrinolytic system with excessive production of PICs, DAMPS and fibrin deposition [44,55,56]. This is described as immuno-thrombosis [44,55,56]. This state has a major pathophysiological role in the development and exacerbation of systemic sepsis as it generates the formation of vascular microthrombi, and is responsible the development of DIC and subsequent multi-organ damage or failure [57–59].

The sequestration of platelet neutrophil complexes in the pulmonary vasculature and the subsequent development of immunothrombosis is also the ultimate cause of micro-thrombi and micro-emboli in the alveocapilary circulation [60,61], intra alveolar fibrin deposits [44,62–65] and in some circumstances the development of DIC. Readers interested in further details are referred to Gando Otomo [66] and Ito [67]. The translocation of NET producing neutrophils into alveoli and interstitial lung tissue also plays a dominant role in the development of an intrapulmonary cytokine storm ultimately leading to the massive levels of lung tissue damage characteristic of COVID-19 ARDS.

In the context of ARDS accumulating data suggests that the self-amplifying cascade of PIC ROS and DAMP production leads to the activation of the NLRP3 inflammasome and the release of IL-1 and IL-18 [68,69]. This is increasingly considered to be an irrevocable step in the development of ARDS and high levels of NLRP3 inflammasome activity associated with a grave prognosis [70–72]. It is however encouraging to note that the inhibition of NLRP3 assembly is associated with increased rates of survival [73,74] (reviewed by Danielski et al. [75]).

Increased levels of IL-1 and IL-18 appear to make independent contributions to the development of ARDS [70–72] but perhaps the most important consequences of unrestrained NLRP3 activation is excessive levels of alveolar macrophage pyroptosis [76–79] which is another important marker of mortality in ARDS [80].

This association is explained by the release of large quantities of DAMPS, PICs and ROS and the recruitment of PIC and ROS producing bone derived monocytes from the periphery [81,82] leading to extensive RIPK mediated necroptosis [38,43]. Importantly, this mode of programmed cell death releases massive amounts of HGMB1, mtDNA, PICs ROS and chemokines forming an autoinflammatory loop described as necroinflammation [83,84] and irreversible lung failure [85]. Crucially, the existence of widespread necroptosis is an acknowledged cause of irreversible lung failure [85] and is predictive of non-resolving ARDS and mortality in patients on mechanical ventilation [38,43]. The processes described above are summarised in Fig. 1.

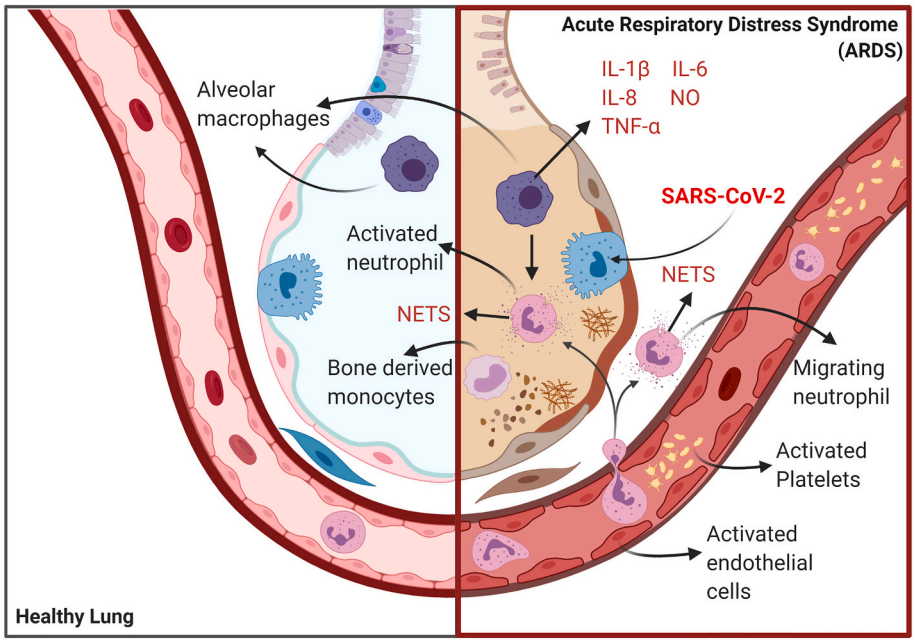

Fig. 1. The pathophysiology of COVID-19 ARDS. Initial infection and activation of type 2 alveolar cells and alveolar macrophages by SARS-CoV-2 results in the secretion of IL-6, PICs, NO and several chemokines which activate vascular endothelial cells platelets and neutrophils ultimately forming a platelet neutrophil complex. The interplay between vascular endothelial cells activated platelets and activated primed neutrophils produces a highly coagulative and inflammatory state described as immunothrombosis. The translocation of neutrophils and platelets into the pulmonary microvasculature results in severe epithelial layer damage alveolar fibrin deposition and the formation of microthrombi. The translocation of NET producing neutrophils into alveoli and lung interstitium coupled with their delayed apoptosis results in the development cytokine storm producing extreme tissue damage and often fatal lung dysfunction created by several feed-forward loops involving interplay between PICS DAMPS ROS, activation of the NLRP3 inflammasome activation, alveolar macrophage pyroptosis, influx of inflammatory bone derived monocytes and necroptosis.

4. Suggestions for therapeutic intervention

4.1. Zinc

Patients with severe infections and/or experiencing systemic inflammatory response syndrome (SIRS) often present with up to a five-fold reduction in plasma Zn compared to healthy controls due to a redistribution of the ions into the liver [86–89]. Importantly, such a reduction in Zn levels is predictive of increased mortality and the extent of reduction correlates negatively with levels of inflammation, increased severity of symptoms and damage to the heart and other organs [86,90,91]. Due to this, Zn levels have been suggested as a diagnostic marker of SIRS/sepsis and likelihood of mortality [90].

Mechanistically, evidence suggests that this state of affairs seen in an environment of excessive systemic inflammation, stems from increased activity and levels of ZIP-14 and ZIP-8, two promiscuous members of the SLC-39A family of Zn transporters, which stimulate the uptake of Zn from the plasma into the liver [92–94]. This phenomenon, commonly observed in a state of excessive inflammation, is driven by elevated levels of IL-6, lipopolysaccharide (LPS), IL-1 and nitric oxide (NO) which increase the activity of the transcription factors AP-1 and ATF-4, resulting in increased uptake of Zn into the liver resulting in state of hypozincaemia [92–94].

Importantly, grossly reduced levels of plasma Zn results in a compromised and dysfunctional response to pathogen invasion by the innate and humoral branches of the immune system [95–97]. Typically, and perhaps paradoxically, the results of depleted Zn influenced immune dysfunction in sepsis patients [87] manifests as an exacerbated inflammatory response associated with increased activity of NF-κB, excessive levels of PIC production, oxidative damage to tissues and massive levels of leucocyte death [86,98–100]. From a pathophysiological perspective, it is important to note that these factors seen in patients in the early stages of SIRS and sepsis development appear to be associated with significant increases in mortality [91,98].

Data also suggests that another important factor associated with increased mortality in sepsis patients is elevated levels of NF-κB activity, most notably in the lungs [98,101]. In this context, it is encouraging to note that Zn supplementation may reduce NF-κB activity in vivo either directly or by inhibiting the STAT-3-NF-κB signalling pathway [91,101,102]. Data from animal studies also suggests that Zn supplementation may restore immune homeostasis in patients experiencing severe systemic inflammation and inhibit the development of sepsis and ARDS [103,104].

The importance of Zn deficiency in the development of ARDS has also been emphasised by the results of a recent paper that reported reduced levels of this ion in intensive care unit patients who went on to develop ARDS compared to those who did not [105]. Moreover, these authors concluded that low levels of Zn predisposed to ventilator induced lung injury [105].

Finally, from the perspective of immune modulation, there is some evidence to suggest that Zn deficiency may exacerbate NLRP3 activity and increase levels of IL-1 beta [106,107].The mechanism underpinning this phenomenon is not completely understood but increased lysosomal permeability in a cellular environment of chronic Zn deficiency may be a contributing factor [107]. Zn is also one of the few supplements with credible evidence of anti-viral actions and given the paucity of such candidates we focus on this area below.

There is evidence that high levels of Zn salts may inhibit the essential RNA dependent RNA polymerase (RdRp) enzyme, which is conserved in all coronaviruses [108]. It appears that this property may extend to the respiratory syncytial virus (RSV), rhinoviruses, hepatitis E, dengue, West Nile and Zika viruses whose RdRp is almost identical to the equivalent enzyme in coronaviruses [109–112]. The inhibitory influence of excess Zn appears to the fact that these RdRp are in effect protein metallothionines dependent on an intricate quantum relationship between bound Zn and magnesium for their activity. This relationship appears to be disturbed in a cellular environment of excess Zn ions [113,114]. In vitro evidence suggesting that Zn chelation may inhibit the RNA dependent RNA polymerase of COVID-19, effectively halting the replication of the virus, has understandably stimulated a great deal of interest in Zn supplementation as a means of inhibiting the replication of COVID-19 in vivo [108].

4.2. Azithromycin

There is a large and accumulating body of evidence demonstrating significant improvements in patients suffering from a range of serious lung diseases following the long term administration of azithromycin (AZM) and other macrolide antibiotics (reviewed by Faverio et al. [115]). Importantly, in the case of AZM, such evidence extends to

reducing mortality in patients suffering from ARDS secondary to a range of insults or sepsis [116,117]. For example, Kawamura et al. [116] engaged in a retrospective review of outcomes in 191 ARDS patients and reported a statistically significant improvement in the 60 days survival of patients prescribed AZM compared to those on standard care only. This was also accompanied by reduced time on ventilation [116]. The results of this study echoed earlier work by this team of authors with almost identical outcomes in patients with ARDS induced by sepsis [117]. Importantly, significant reductions in mortality following AZM therapy has also been reported in patients suffering from acute lung injury [118]. In addition, a large meta-analysis of prospective studies involving over 70,000 elderly patients hospitalised with pneumonia also reported a significant improvement in mortality in these individuals prescribed AZM compared to those who had not been given this medicine on admission to hospital [119].

There is a growing appreciation that the benefits accrued by patients following the administration of AZM and other macrolide antibiotics is due to their pleiotropic immunomodulatory properties. A recent meta-analysis concluded that over time the administration of these molecules resulted in reduced levels of chemokines, most notably IL-8, decreasing molecular adhesion (E-selectin, ICAM-1), integrins (CD11b/CD18), reduced levels of PICs, inhibition of neutrophil and eosinophil function, decreased effector T cell activity and reduced levels of matrix metalloproteinase 9 [120].

From the perspective of a potential treatment for ARDS, it should be noted that AZM accumulates in alveolar macrophages and neutrophils to a far greater degree than any other macrolide and levels of the antibiotic within these immune cells may be 2000 times greater than levels found in the plasma following short term or long term administration [121,122]. This is of importance as evidence suggests that AZM is a highly effective NF-κB inhibitor in vivo [123,124]. Hence, AZM offers an option to inhibit NF-κB in a highly targeted manner.

Several human and animal studies have also reported a profound change in the polarisation of activated alveolar macrophages from the highly inflammatory M1 phenotype to the anti-inflammatory M2 phenotype following prolonged treatment with AZM for a range of pulmonary and autoimmune illnesses [125–129]. These changes are characterised by significant changes in the transcriptome of AMs as evidenced by the upregulation of CCL18, fibronectin, arginase 1 and a decrease in the production of Matrix metallopeptidase 9 (MMP-9), inducible nitric oxide synthase 2 (NOS2) and PICs due to the inhibition of STAT-1 and reduced translocation of NF-κB [125–127]. Ultimately, the positive effects of AZM on AM polarisation appears to be via the stimulation of PI3/Akt/mTor signalling, which inhibits the activity of NF-κB and stimulates the expression of genes involved in the transition between the inflammatory and anti-inflammatory phenotypes [129–133]. The activation of the phosphoinositide 3-kinase (PI3K) signalling pathway is also associated with increased AM efferocytosis [134], and reports of improved AM phagocytosis following AZM therapy are unsurprising [135–137].

AZM also appears to induce the recruitment of $CD11b^{+}$ $Gr\text{-}1^{+}$ myeloid-derived suppressor cells (MDSC) into the lung [126] and this seems to be a general property of macrolides [138]. This is important, as MDSCs are potent suppressors of T cell responses and evidence suggests that they play an important role in ameliorating damage to lung tissue following severe pneumonia or the advent of septic shock [138,139] (reviewed by Alshetaiwi et al. [140]). The combined effects of AZM on AMs and MDSCs go some distance to explaining the reduction in lung tissue damage and inflammation reported following chronic administration of this antibiotic [141–145].

In addition, there is ample evidence to suggest that chronic AZM therapy results in reduced neutrophil infiltration into the lungs and ameliorates pre-existing neutrophilia [146–149]. This appears to be largely due to decreased IL-8 production by alveolar macrophages and epithelial cells, although there is some suggestion that decreased IL-8 production by alveolar myofibroblasts may also be involved [144,145,149,150].

Prolonged AZM treatment also has profound effects on neutrophil function and survival leading to significant and large decreases in PIC production and survival [151–154]. The anti-inflammatory effect of AZM on neutrophil performance appears to be mainly mediated by PI3K mediated inhibition of NF-kB in a similar manner to the anti-inflammatory effects on AMs. In some respects, this can also be said of increased neutrophil apoptosis as a result of decreased levels of IL-6 and IL-8, which would otherwise increase neutrophil survival. However, decreased neutrophil survival following AZM administration also appears to be mediated by the inhibition of GM-CSF [155,156]. This cytokine regulates many aspects of neutrophil function and decreased levels inhibit neutrophil priming, which is important in the development of ARDS [155]. In addition GM-CSF downregulation appears to be responsible for the neutrophil recognition of chemotactic stimuli, which is important in reducing the recruitment of activated neutrophils into inflamed lung tissue [122]. The downregulation of this cytokine is also an important therapeutic benefit as there is evidence that elevated levels of GM-CSF is a major contributor to extensive lung damage and increased mortality in severe pneumonia [157,158].

Finally, there is evidence to suggest that AZM inhibits the activity of the NLRP3 inflammasome and the subsequent release of IL-1 beta [121,159]. Moreover, there is evidence that AZM decreases the stability of NLRP3 mRNA likely via a direct effect on ribosomes [159] which is a different mechanism than in the case of Zn suggesting that the use of Zn and AZM in combination might produce additive or synergistic results.

4.3. Aspirin

Three recent meta-analyses have reported significantly increased survival in ARDS patients prescribed aspirin compared to those who were aspirin free [160–162]. Furthermore, the effect appear to be greater in critically ill patients and patients with ARDS-related sepsis than a wider group of patients [160,161]. Pertinently, there is also data to suggest that aspirin prophylaxis might also reduce the severity of ARDS and result in a substantial reduction in long term mortality (reviewed by Wang et al. [162]).

Several research teams have also reported reduced mortality in patients over 65 presenting at hospital with severe pneumonia prescribed aspirin compared to those who were aspirin naive [163–165]. For example, Falcone et al. reported a four-fold reduction in mortality in aspirin treated patients suffering from severe pneumonia compared to controls [163]. Importantly, this was a large study containing 390 patients in the aspirin arm and 614 aspirin free [163]. Similar results have been provided from earlier studies where patients ingesting aspirin in the community or administered the drug at the point of hospital admission demonstrated significantly reduced mortality especially in patients with severe symptoms and or those who became critically ill [164,165]. Given that aspirin use in the community may be associated with greater health literacy and other adaptive health behaviours, these confounders may need to be borne in mind.

The presence of activated platelets in patients suffering from viral pneumonia or a severe upper respiratory tract infection is a well-documented [166–168]. In addition, platelet activation is associated with a higher risk of myocardial infarction and cardiovascular related mortality seen in this group of patients [166,169]. Hence it seems reasonable to suggest that at least some of the potential benefits of aspirin to this group of patients may be mediated by the anti-platelet effects of aspirin. These are generally attributed to the irreversible acetylation of cyclooxygenase (COX) 1 and the long-term inhibition of thromboxane A2 [170].

Aspirin also exerts a range of beneficial effects on the coagulation cascade and the prevention of thrombosis in addition to inhibiting COX1 (reviewed by Patrono [171]). Several mechanisms appear to be involved including reducing tissue factor production by platelets and immune cells with the acetylation of thrombin and prothrombin also playing an

important role [172] (reviewed by Undas et al. [173]). In addition, high dose aspirin (greater than 300 mg/day) appears to increase the efficiency of fibrinolysis [174,175]. Ingestion of aspirin also leads to the upregulation of lipoxin A4 in humans and animals [176–179] via a mechanism involving the irreversible acetylation of COX2 [180,181] (reviewed by Romano et al. [182]). This is an important consequence of aspirin as these molecules play major role in the resolution of inflammation in conditions such as sepsis and ARDS [65,183]. Importantly, aspirin is the only nonsteroidal anti-inflammatory drug capable of activating lipoxins in immune, endothelial and epithelial cells and the only trigger of lipoxin A4 production by platelets [181].

The role of lipoxin A4 in the resolution of acute lung damage and ARDS are multiple. For example, it is involved in the repair of pulmonary epithelium by stimulating the trans-differentiation of alveolar type 2 cells into alveolar type 1 cells and the recruitment of the former from distal tissue [184,185] (reviewed by Chandrasekharan and Sharma-Walia [186]). In addition, the upregulation of this molecule in neutrophils and macrophages also reduces the activity migration priming of the former and the efficiency of phagocytosis and activity of the latter [185,187]. Upregulation of lipoxin A4 also induces a wide range of anti-inflammatory effects stemming from reductions in TNF-alpha [179], increased SOCS2 [188], decreased translocation of HGMB1 [189] and inhibition of NF-κB [189–191].

Finally, there is evidence that aspirin administration inhibits the activation of the NLP3 inflammasome [192–194]. In addition, this may be a specific property of aspirin and may underpin a significant improvement in endothelial function [192,194]. This data raises questions regarding the appropriate dose of aspirin for consideration in a trial of a treatment for COVID-19. In particular, 75 mg/day would appear to have little or no effect on COX2 inhibition, and significant NF-κB inhibition would appear to require doses in excess of 300 mg per day and would seem to be optimal at 1500 mg per day [195,196]. It is possible that the doses of aspirin required may rival those used in the treatment of rheumatic fever [197].

4.4. *N-acetylcysteine (NAC)*

Oral and intravenous NAC administration has demonstrated clinical efficacy in patients suffering from a wide range of chronic refractory respiratory illnesses including chronic bronchitis [198–200], chronic obstructive pulmonary disease [201–204], cystic fibrosis, bacterial biofilms [205], asthma, pulmonary fibrosis and allergies [206–208]. There has also been interest in NAC as a treatment for ARDS and two recent meta analyses concluded that NAC reduced the need for ventilation and shortened ventilation time, although no reductions in mortality have been reported [209,210]. However, a reduction in the need for ventilation is a major therapeutic benefit as ARDS patients may suffer long term physical and psychological morbidity which are associated with significant health care costs [211]. In addition, NAC supplementation appears to ameliorate many elements involved in the pathophysiology of ARDS. For example, NAC supplementation decreases neutrophil recruitment and activity while increasing neutrophil apoptosis in an environment of intense lung inflammation [212–216]. The increased levels of neutrophil apoptosis seen following NAC administration appears to be due to increased efferocytosis of AMs which appears to be secondary to improved redox status [214,217]. In addition, evidence suggests that NAC also reduces levels of platelet, monocyte and neutrophil complexes in vivo [218,219]. Furthermore, several studies have reported that NAC supplementation results in a reduction in neutrophil production of NETs [218,220,221].

Evidence from human studies also suggests that NAC reduces levels of platelet monocyte and neutrophil complexes in vivo [218,219]. Several authors have also reported significant reductions in levels of pulmonary inflammation following NAC supplementation at approximately 1200 mg/day as evidenced by reduced levels of PICs, ROS, tissue damage and fibrin deposits in alveoli and interstitial tissue [222–224]. There is also evidence to suggest that *NAC* improves pulmonary function, an effect which appears to be enhanced when the thiol is inhaled [207,225]. NAC supplementation also exerts several other anti-inflammatory effects relevant to the pathophysiology of ARDS, most notably by decreasing levels of IL-6 [226–228] and NF-κB [229–231].

Finally, authors of a prospective double blind RCT investigating the use of 1200 mg/day in mechanically ventilated patients reported, that compared to placebo, patients administered NAC were less likely to develop ventilator associated pneumonia (VAP), had a significantly reduced stay in intensive care unit and an increased incidence of complete recovery [232]. This may be of significance from the perspective of treating COVID-19 ARDS as VAP may well be a significant cause of long term morbidity and mortality in patients requiring mechanical ventilation despite improvements made by prone positioning [233].

Several research teams have reported reduced endothelial cell activation and improved endothelial function following supplementation with oral NAC [234–236]. Interestingly, the mechanism appears to involve inhibition of the NLRP3 inflammasome [237–239]. In addition significant inhibition of platelet activity has been reported in in patients with type 2 diabetes and in healthy volunteers [240–243], which appears to be secondary to increased levels of intraplatelet glutathione and production of NO with a concomitant reduction in levels of oxidative stress [243].

In addition, evidence suggests that NAC inhibits the development of large vessel thrombosis in inflammatory illnesses such as diabetes [243] and may even reduce thrombus formation to a similar degree to the effect produced by low dose aspirin [218]. Intravenous NAC administration promotes lysis of arterial thrombi in patients who are resistant to antiplatelet thrombin inhibitors and recombinant tissue-type plasminogen activator targeting VWF [244,245]. Such data has increased interest in the use NAC in patients displaying evidence of aspirin resistance despite being prescribed a dose known to inhibit thromboxane A2 [246,247].

It is important to stress that the anticoagulant and platelet-inhibiting properties of NAC are seen in in patients with serious conditions such as those undergoing major vascular surgery [248]. It is also noteworthy that the anticoagulant effects of NAC extend to decreasing the activity of coagulation factors II, VII and X, thereby producing a significant decrease in prothrombin time [249,250]. These properties have led to an increased focus on an expanded role of NAC in the inhibition of platelet aggregation in the context of reperfusion injury in recent years (reviewed by Nikbakht et al. [251]). Some of the mechanisms underpinning the effects of NAC on the coagulation and fibrinolytic systems ultimately leading to decreased thrombus formation have been discussed above. However a reader interested in an in depth consideration of the area are referred to an excellent review by Gutmann et al. [252].

The weight of evidence suggests that severe vitamin (Vit) D deficiency is a common occurrence in intensive care unit (ICU) patients with sepsis, septic shock and ARDS [253,254]. In addition, several authors have reported positive correlations between Vit D levels and increasing illness severity [253–255]. The extent of Vit D depletion also appears to be predictive of increased mortality reviewed [256]. It is also noteworthy that the level of Vit D depletion on admission to hospital is also predictive of developing severe disease and poor outcomes [257,258].

The relationship between low Vit D levels and increased severity of sepsis, appears to be due, at least in part, to exaggerated levels of inflammation and immune activation compared to patients with adequate levels of this vitamin [259–261]. This phenomenon may well exist in other illnesses whose pathophysiology involves chronic systemic immune activation and inflammation [259–261]. In fact several human studies investigating Vit D levels in conditions such as type 2 diabetes and metabolic syndrome have reported higher activity of NF-κB and increased levels of PICs in patients with Vit D deficiency compared to those whose level of the vitamin is within normal limits [262–266]. These findings are consistent with other lines of evidence suggesting that Vit D plays an indispensable role in modulating inflammation and

adequate levels are needed for an optimal anti-inflammatory response to prevent an over exuberant immune response to invading pathogens or sterile insults [267–269]. Unsurprisingly Vit D exerts a wide range of broadly tolerogenic effects on the immune response via engagement with the Vit D receptor and these are summarised in Fig. 2.

Several human studies confirming a beneficial effect of Vit D on NF-κB activity and levels of PICs most notably TNF-alpha and IL-6 [262–266] reviewed. It is also noteworthy that a recent double blind RCT. Ventilated patients using a dose of Vit D in the range of 250,000 to 500,000 IU (55 ng/ml) over 7 days reported clinically significant reductions hospital stay suggesting that the dose needed to treat COVID-19 ARDS is likely to be of the same order [270].The issue of dosage as also addressed in a recent meta-analysis investigating the use of Vit D in the treatment or prophylaxis of respiratory virus infections which reported significant benefit at levels greater than 40 ng/ml but no evidence of benefit at lower doses [271] reviewed [272]. There is some evidence that Vit D supplementation may improve the immune status in patients with HIV [273] dengue [274] and hepatitis B infections [275].

There is evidence that Vit D supplementation may decrease the replication of rhinoviruses via a mechanism involving the upregulation of the interferon response and cathelicidin (LL-37) in lung epithelial cells [276,277]. LL-37 upregulation appears to be a major element involved in the anti-viral defences of lung epithelial cells and this also appears to be true of macrophages and dendritic cells. Importantly, there is also evidence to suggest that LL-37 upregulation may inhibit the replication of herpes simplex virus type one (HSV-1), respiratory syncytial virus (RSV) vaccinia virus HIV and HTLV-1, H1N1 and Ebola [278–281]. Unsurprisingly, given the information above depleted levels of Vit D are associated with sub optimal LL-37 expression in lung epithelial cells which are a known target for SARS-CoV-2 entry [278].

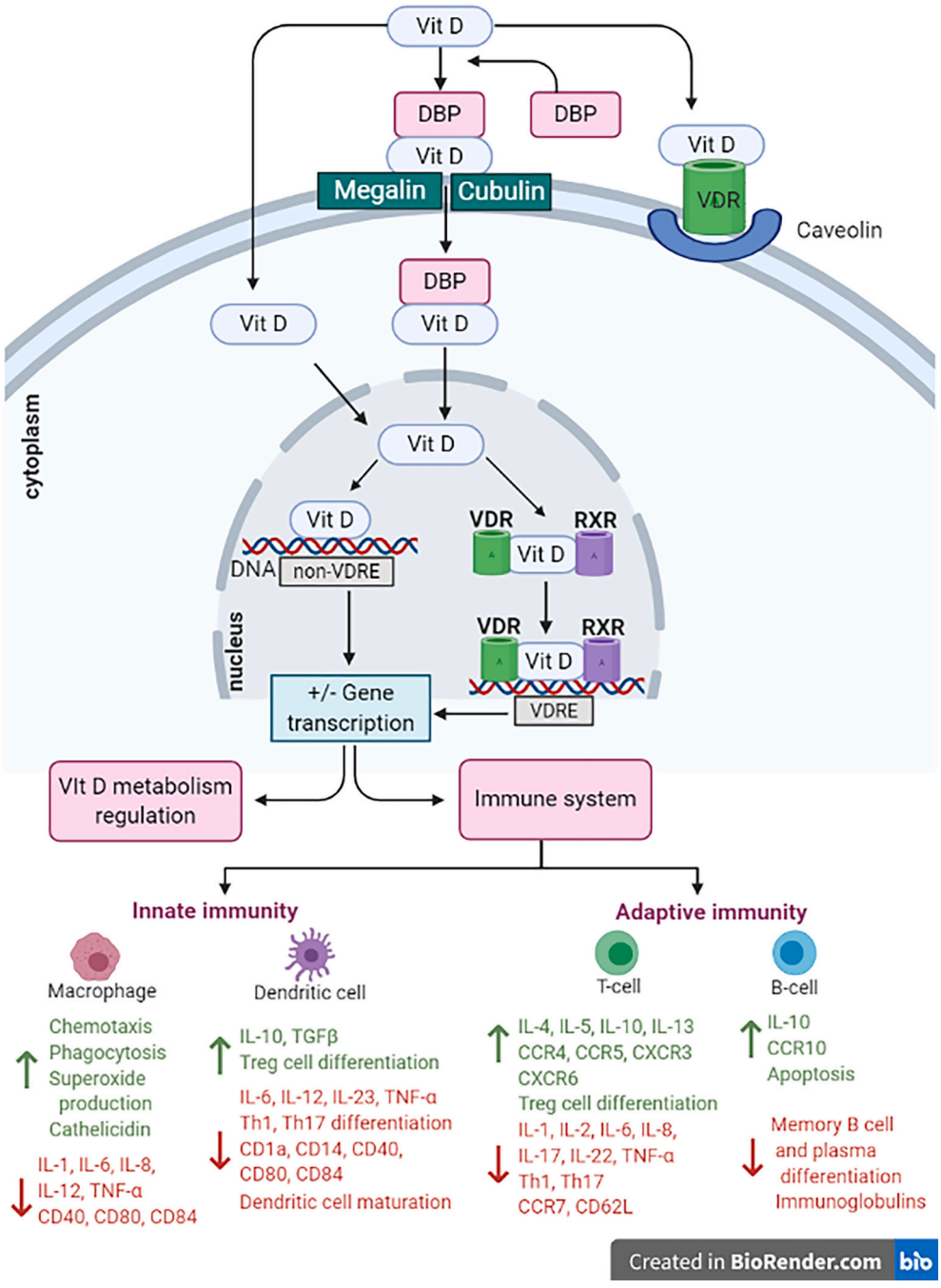

Fig. 2. The effects of vitamin D on the immune system. Vitamin D inhibits B cell proliferation differentiation and immunoglobulin secretion. Vitamin D also suppresses T cell proliferation, TH17 differentiation increases levels of regulatory T cells and induces a tolerogenic Th2 phenotype. The sum of these effects is reduced levels of interleukin (IL)-17, IL-21 and IL-23 and increased levels of IL-10. Vitamin D also inhibits the maturation of dendritic cells and inhibits the production of pro inflammatory cytokines and chemokines from monocytes and macrophages reducing plasma levels of TNF-alpha, IL-1, IL-6, IL-12 and IL-8. In addition, Vitamin D activity stimulates the production of beta defensins and cathelicidin in monocytes and macrophages following pathogen invasion with forms an essential role in the anti-viral response.

Hence when considered as a whole this data combined with the multiple lines of evidence discussed above support the use of Vit D as part of a rational treatment approach for COVID-19. Finally, Vit D acts in alliance with many other molecules and systems when exerting its effects on the immune response and hence potential synergies may exist when combined with other molecular players such as melatonin reviewed [282]. Readers interested in a detailed consideration of the role of LL-37 in the pulmonary immune response to infection are referred to the work of [283].

4.5. Vitamin C

Levels of Vit C, otherwise known as ascorbic acid, are grossly depleted in many patients with severe infections sepsis and septic shock despite being administered adequate levels of enteral or parenteral nutritional therapy [284–287]. Mechanistically this state of affairs appears to be due to increased consumption due to high levels of oxidative stress [284,286] and the inhibitory effect of PICs on the sodium dependent Vit C transporter (SVCT) 2 [288,289]. This receptor is expressed in most cells and responsible for the cellular entry of ascorbate [288,289]. Readers interested in a more detailed consideration of this topic are invited to consult a thorough review of the area in Mangin et al. [290].

Ascorbate related hypovitaminosis is associated with increased levels of inflammation and compromised immune function in a similar manner to the scenario of severe Vit D depletion [291–293]. Higher levels of inflammation increased activity of NF-κB increased production of NETs and increased neutrophil netosis [294,295]. Vit C exerts a range of anti-inflammatory effects on the immune system via the modulation of hypoxia inducible factor alpha (HIFalpha) levels and levels of histone acetylation and DNA methylation via regulating the activity of ten eleven translocase (TET) and proteins containing a Jumonyi C (JDHM) domain [284,296,297]. A summary of the phenotypic changes in the immune response induced by the activity of Vit C and the mechanisms involved is included in Fig. 3.

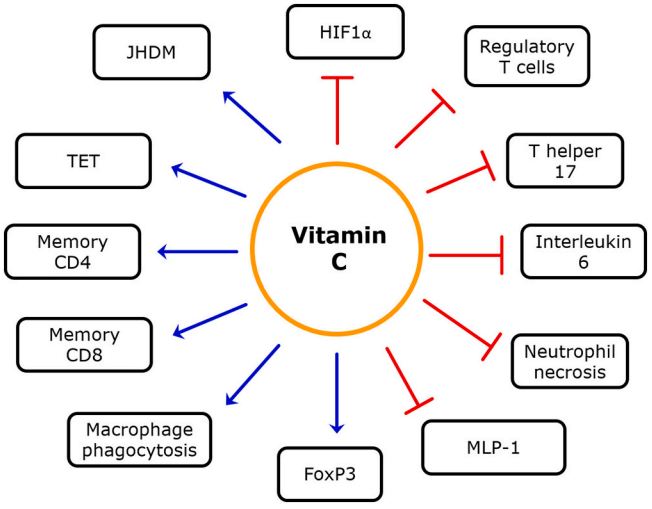

Fig. 3. The effects of Vitamin C on the immune system. Vitamin C enhances the activity of TET enzymes and Jumonji C domain-containing histone demethylases (JHDMs) thereby decreasing rates of DNA and histone methylation respectively and prevents the hyperactivity of HIF 1 alpha. The net effect of these actions involves increased macrophage phagocytosis decreased neutrophil necrosis and the differentiation of T cells into a TH2 phenotype increases levels of regulatory T cells and inhibits naive T cell differentiation into a Th17 phenotype. Vitamin C is needed for memory CD8 and CD4 T cell formation and optimal T lymphocyte function. Vitamin C supplementation also reduces IL-6 and MCP-1 production by macrophages and dendritic cells while inhibiting dendritic cell maturation.

The bioavailability of oral form of Vit C are limited by the activity of SVCT1 which appears to reach saturation level in the dose range of 500-1000 mg limiting plasma levels to approximately 220 μmol/ml. However, the use of IV administration bypasses the limitations of this receptors leading to plasma levels of Vit C which are some 70 times higher at 15,000 μmol/ml [298,299] suggesting that the IV formulation would be the one of choice in any intervention aiming to treat COVID-19. This point is reinforced by data supplied by the citrus study reporting that IV Vit C administration at 200 mg/kg 4 days resulted in significant reduction in hospital stay and overall mortality in ventilated ARDS patients [300]. In addition the oral doses of Vit C needed to produce evidence of therapeutic benefit in this patient group would appear to be in excess of 6 g/day although at these doses data suggests that ventilation time in ARDS patients may be reduced by 25% review [301]. In addition, there is growing interest in combining Vit C, thiamine and hydrocortisone as a treatment for sepsis and ARDS following the results of a recent study where the use of these preparations in unison resulted in a 25% reduction in mortality [302].

Finally, there is evidence to suggest that high dose IV Vit C inhibits the replication of rhinoviruses [303], H1N1 [304], Chikungunya [305], Zika [305] and seasonal influenza [306]. In addition there is also some evidence that oral supplementation with Vit C (doses over 3 g) may also reduce the risk of infection by prevent respiratory viruses [291].

4.6. Dexamethasone

Dexamethasone exerts its anti-inflammatory effects by upregulating the activity of glucocorticoid receptors (GR) and inhibiting the activity of a number of proinflammatory transcription factors including NF-κB reviewed [307]. This is an important point as the weight of histopathological evidence suggests that non resolving ARDS is associated with increased activity of nuclear NF-κB and decreased activity of nuclear GRs [308,309]. In the light of this data and the potential decrease in mortality in patients suffering from COVID-19 ARDS following dexamethasone administration and its mechanism of action is briefly considered below.

Following diffusion across the cell membrane dexamethasone and indeed other glucocorticoids bind to the cytosolic GR resulting in a conformational change freeing the GR from the constraints of a heat shock chaperone [310]. The unencumbered GR then translocate to the nucleus and bind to glucocorticoid-responsive elements (GREs) located in the promoter regions of proinflammatory and anti-inflammatory genes increasing the transcription of the latter and decreasing the transcription of the former by *cis*-activation or *cis*-repression respectively [311,312]. These mechanisms are reviewed in Xavier et al. [313]. GRs may also engage with other transcription factors in the nucleus limiting or modifying their DNA binding activity by various mechanisms such as competing for the same indispensable cofactor and may also act posttranscriptional by modifying the stability of mRNA [312] (reviewed in Laryea et al. [314]).

Dexamethasone upregulated GR activity mediates NF-κB inhibition by increasing the production and inhibiting the degradation IκBα which sequesters NF-κB in the cytoplasm via direct effects on the GRE sequence in the IκBα gene and in the gene responsible for the production of IL-10. The use of dexamethasone also results in the formation of GR-NF-κB complexes in the nucleus resulting in the reduced activity of NF-κB due to restricted access to the indispensable cofactors steroid receptor coactivator-1 (SRC-1) and CREB-binding protein (CBP). Several authors have also reported increased expression of mitogen-activated protein kinase phosphatase-1 (MKP-1) in lung epithelial cells following dexamethasone administration at physiological concentrations [315,316] This has the effect of decreasing the activity of MAP kinase which plays an indispensable role in IL-1 and TNF-alpha mediated increases in the activity of NF-κB [315,316].This data is of particular interest as this may be an effect which is unique to this steroid and may underpin significant depression in pulmonary IL-8 levels following its administration

[317,318]. Finally, there is also evidence to suggest that dexamethasone ligated GRs form complexes with p65 NF-κB subunits in the cytoplasm which ultimately translocate to the nucleus exhibiting greater anti-inflammatory activity and inducing increased production of anti-inflammatory proteins such as A20 compared to GR receptors acting alone [319,320].

Dexamethasone may have value in COVD-19 characterised by a cytokine storm. Dexamethasone has potent anti-inflammatory effects that are dose related. It inhibits LPS-stimulated TNF-alpha release, as well as levels of IL-6, IL-8 and of IL-10 [321]. In bacterial community acquired pneumonia, dexamethasone compared to placebo significantly lowered levels of f IL-6, IL-8, monocyte chemoattractant protein-1 (MCP-1) and TNF-alpha [322]. Timing appears to be a critical factor, as corticosteroids may have value in severe SARS-CoV-2 infection characterised by the presence of the hyperinflammation phase of a cytokine storm [34]. In early and milder disease, viral clearance can be delayed and inhibited, resulting in poorer outcomes. Evidence of this derives from the SARS experience, where a 20.7-fold higher risk of ICU admission was seen with the routine use of steroids [323]. Similarly, during the middle east respiratory syndrome (MERS) epidemic, corticosteroid therapy worsened outcomes due to delayed clearance of MERS coronavirus [324]. The extant data from the COVID-19 pandemic suggests that use of steroids in non-critical patients without a cytokine storm is not advisable [325]. Dexamethasone may have benefit in ventilator induced lung injury [326]. There are case reports of the use of dexamethasone in the treatment of SARS-CoV-2 pneumonia complicated by pulmonary oedema resulting from the pulmonary capillary leak syndrome [327]. Preliminary non-peer reviewed data from the Randomised Evaluation of COVID-19 (RECOVERY) trial suggests a benefit in people with severe COVID-19 infection on ventilators in ICU (2020).

5. Conclusion

A comprehensive and highly plausible model has been proposed in this paper detailing the pathophysiological steps of COVID-19 from the point of initial infection of type II alveolar epithelial cells by SARS-CoV-2 to the ultimate development of ARDS. This model highlights are various several potential control points where targeted therapeutic interventions might produce significant benefits in reducing the severity of disease. Several lines of evidence suggest a role for dexamethasone for the treatment of ARDS. In addition, consideration of data supplied by human an animal studies also highlight the potential efficacy of Zn supplementation, aspirin (acetylsalicylic acid), the macrolide antibiotic azithromycin, oral or intravenous administration of NAC, IV Vit C and oral Vit D. Moreover, when used at appropriate doses, these supplements and drugs generally have an exceptionally good safety record. Hence, based on this evidence, it is recommended that randomised trials of these therapeutic substances in COVID-19 are in order. Given that excessive levels systemic inflammation seen in patients with severe COVID-19 is likely to lead to depleted levels of Vit C, Vit D and Zn in many individuals and significant differences in their mode of action as anti-inflammatory agents, it is suggested that they should be used in combination. Equally, the use of aspirin at a dose in excess of 300 mg, NAC and AZM offers the prospect of localised NF-κB inhibition and reducing the activation of the coagulation cascade characteristic of severe COVID-19.

List of abbreviations

AM	alveolar macrophages
ARDS	acute respiratory distress syndrome
AZM	azithromycin
CBP	CREB-binding protein
COX	cyclooxygenase
DAMPS	damage-associated molecular patterns
DIC	disseminated intravascular coagulation
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GR	glucocorticoid receptor
GREs	glucocorticoid-responsive elements
HIPalpha	hypoxia inducible factor alpha
HMBG1	high mobility group box 1
HSV-1	herpes simplex virus type one
ICU	intensive care unit
IL	interleukin
JDHM	Jumonyi C
LPS	Lipopolysaccharide
MCP-1	monocyte chemoattractant protein-1
MDSC	CD11b + Gr-1+ myeloid-derived suppressor cells
MERS	middle east respiratory syndrome
MKP-1	mitogen-activated protein kinase phosphatase-1
MMP-9	matrix metallopeptidase 9
mtDNA	mitocondrial DNA
NAC	*N*-acetylcysteine
NETs	neutrophil extracellular traps
NF-kB	Nuclear Factor kappa-light-chain-enhancer of activated B cells
NLRs	NOD-like receptors
NO	nitric oxide
NOS2	inducible nitric oxide synthase 2
PI3K	phosphoinositide 3-kinase
PICs	proinflammatory cytokines
RCT	randomised controlled trial
RdRp	RNA dependent RNA polymerase
ROS	reactive oxygen species
RSV	respiratory syncytial virus
SARS-CoV-2	severe acute respiratory syndrome CoronaVirus 2
SIRS	systemic inflammatory response syndrome
SRC-1	steroid receptor coactivator-1
SVCT	sodium dependent Vit C transporter
TET	ten eleven translocases
TLR	Toll-like receptor 9
TNF	tumour necrosis factor
VAP	ventilator associated pneumonia
VIT	vitamin
Zn	zinc

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

CRediT authorship contribution statement

GM conceptualized the work and was a major contributor in writing the manuscript. CCB created the figures. All authors have drafted part and approved the final manuscript.

Declaration of competing interest

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