REVIEW ARTICLE

AVIPTADIL; Class effect of a Synthetic VIP as a treatment option in COVID 19 patients with severe respiratory failure

Dwaipayan Sarathi Chakraborty[1], Shouvik Choudhury[2], Sandeep Lahiry[3]

¹Diamond Harbour Govt. Medical College, Department of Pharmacology, West Bengal, India
²Burdwan Medical College, Department of Pharmacology, West Bengal, India
³Independent Research Scholar, West Bengal, India

Abstract

Despite dynamic drug and vaccine developmental processes to reduce the disease burden of COVID 19, still the options for treatment are very limited. Vasoactive peptide (VIP) has diversified physiological action with specific features of lung protection-related activities. VIP inhibits SARS COV-2 gene replication in human monocytes and viral replication in Calu -3 cells thus further reducing the generation of proinflammatory mediators Aviptadil, a synthetic form of VIP, is the only pulmonary therapeutic agent to have been granted Fast Track status by the US FDA and to be allowed into both phase 2/3 clinical trials Initial binding of Aviptadil with nsp10 & nsp 16 which may inhibit the 2 -O-MTase activity of the SARS-CoV nsp10/16 complex Aviptadil as a synthetic VIP has already been proved to be an effective option in the treatment of severe respiratory failures due to sepsis and other related lung injuries. Interim analysis results of this drug use in respiratory failures caused by SARS COV-2 has evolved a new hope in regards to safety and efficacy. Final results from recently completed as well as all currently ongoing trials will clarify the class effect of this drug in the treatment of COVID 19 in future days.

Keywords: Pandemic, SARS COV-2, VIP, synthetic, interim

Introduction

COVID 19 has created an unprecedented situation globally over the last 18 months. Globally, as of 23 November 2021, there have been 257.469,528 confirmed cases of COVID-19, including 5.158,211 deaths, reported to WHO. This pandemic has to lead to extensive research to evaluate the safety and efficacy of several repurposed and new drugs. Numerous clinical trials are ongoing as scientific evidence to establish the clinical benefits of those drugs. The mainstay of the treatment continues to be based on supportive care with the possible use of pharmacological agents in patients with more severe illnesses. Antiviral agents like Remdesivir may help in shortening the duration of illness but may not be efficacious enough to provide the survival benefit in life-threatening situations. Hypoxic individuals as well as those requiring supplemental oxygen and/ non -invasive or invasive ventilatory support, treated with low dose steroids have shown improved survival outcomes with robust data supporting the statistically significant clinical outcome parameters. In an adjunct to that, parenteral as well as oral anticoagulants have shown promising results in regards to combatting fatal complications like a pulmonary embolism in cases of moderate-severe illness hospitalized in dedicated isolation wards as well as intensive care settings. Convalescent plasma has not lived up to the promise it holds initially as the recent RCTs failed to demonstrate any added benefit as per as the mortality and morbidities of the disease are concerned. Cytokine inhibitors like Tocilizumab and other immunomodulatory drugs need further evaluation among a larger participating population of clinical trials to establish their efficacy [1].

After performing an extensive literature review using three important databases PubMed, Scopus, and Cochrane it has been found that despite dynamic drug and vaccine developmental processes to reduce the disease burden of COVID 19, the disease may not be eradicated due to the evolution of newer mutant strains of SARS COV2 and logistic challenges in the administration of

*Corresponding Author: Dwaipayan Sarathi Chakraborty, Diamond Harbour Govt. Medical College, Department of Pharmacology, West Bengal, India
E-mail: drdsc2014@gmail.com

vaccines globally at a larger scale. Due to these reasons cornerstone of such disease management remains dependent up to a certain extent on novel drug discoveries and their accelerated regulatory approval to be used on basis of investigational therapeutic tools [2].

Vasoactive Intestinal Peptide (VIP) was first isolated from the hog intestine by Said and Mutt in the year 1970 [3]. It is mainly located in the myenteric and submucosal neurons as well as nerve terminals of the GI tract and contains 28 residue amino acid peptides. Apart from the digestive system, it is widely distributed in both the peripheral and central nervous systems, cardiovascular, respiratory, and reproductive systems. This gut peptide hormone belongs to the glucagon/secretin hormone superfamily and is produced by neuroendocrine cells, macrophages, and both B &T lymphocytes [4,5].

Physiology of VIP—VIP is highly expressed in the lung tissue (Approximately 70%) and nasal mucosa [6]. It exerts its action in the lung tissue via two types of receptors acting as GPCRs--- VIP receptor type 1&2 (VPAC 1& 2) and those receptors also activated by Pituitary Adenylate Cyclase Activating Polypeptide (PACAP) that also belongs to the same family VIP belong to. VPAC 1 receptor is predominantly located in lung tissue and T lymphocytes whereas VPAC 2 is found on smooth muscle, mast cell, and basal part of lung mucosa [7]. VIP binds to Type II Alveolar cell (AT-II) via VPAC 1 receptor [8] and AT-II cells despite comprising only 5% of total lung tissue plays an important role in surfactant production which helps in the maintenance of Type I Alveolar epithelial cells.

VIP augments surfactant production by upregulating the enzyme choline phosphate cytidylyl transferase, which induces the incorporation of methyl choline to phosphatidylcholine--a major component of pulmonary surfactant [9]. Additionally, it induces C Fos protein expression in Type II Alveolar cells as well as upregulates Surfactant Protein A expression both of which ultimately lead to surfactant production [10]. It inhibits apoptosis by blocking the activities of caspase, granzyme B, and Perforin [11,12]. It exerts non-adrenergic non-cholinergic bronchodilatation which is 100 times more potent than isoproterenol as well as 50 times more potent vasodilatation of both systemic and pulmonary arteries than prostacyclin [13,14]. Preclinical experiments in the mouse model have demonstrated their role in reducing ischemia-induced reperfusion injuries [15].

Besides the impact on respiratory physiology, it also has several other significant actions and they are

1) Positive chronotropic, ionotropic, and coronary vasodilatory actions.

2) Secretion of water and electrolyte on GI lumen, pancreatic juice, and bile.

3) Stimulation of pepsinogen secretion

4) Regulation of Prolactin secretion and promoting vaginal lubrication.

5) It inhibits T lymphocyte proliferation [16].

6) Promotes T-helper 2 lymphocytes (Th2) differentiation against T-helper lymphocytes (Th1) & regulatory T cell (T regs) induction [17,18].

7) It downregulates several macrophage-mediated inflammatory cytokines and proinflammatory receptors [19].

8) It plays a role of an inhibitory neurotransmitter of the non-adrenergic, noncholinergic autonomic nervous system [20].

9) It inhibits the synthesis as well as activation of NF-KB which blocks the process of TNF ALPHA generation [21].

The rationality behind of use of VIP in COVID 19

Acute respiratory failure is a major cause of death due to SARS COV-2 infection. In general, it is attributed to cytokine storm preceded by the invasion of the alveolar cell by the virus itself and rupture of that pulmonary epithelial cell. This invasion occurs once the virus enters the Type II alveolar cell via binding with its spike protein to Angiotensin-Converting Enzyme 2 (ACE2) surface receptors located on AT-II cells [22]. AT-II cells express VPAC 1 receptors on its surfaces to which the VIP binds and prevents the process of apoptosis in lung injury [23]. VIP inhibits SARS COV-2 gene replication in human monocytes and viral replication in Calu -3 cells thus further reducing the generation of proinflammatory mediators that play a significant role in tissue injury in the course of the COVID 19 disease process [24].

VIP has demonstrated its beneficial effects on lung injury in several animal models (Table 1). Unlike the Anti IL6 drugs it preserves the surfactant production as well as protects the Type II alveolar cells of the lung [24-26]. Other than the surfactant producing and anti-inflammatory activity, VIP has the property of potentially inhibiting the Fas ligand expression and thereby halting the progression of Fas ligand-mediated cell death [27,28]. Acute lung injury caused by the COVID 19 is also contributed by the degranulation of serine proteases granzymes as well as the formation of perforin protein which induces the rapid death of the target cells [29]. As a proven inhibitor of granzyme and perforin, VIP plays an important role in the prevention of cell death in lung tissue [30].

AVIPTADIL use in clinical practice

Aviptadil is a synthetic form of VIP, also known as RLF-100. It has been designated as an orphan drug by FDA to treat respiratory airway diseases like Asthma, Chronic obstructive airway disease (COPD), cystic fibrosis, pulmonary hypertension, cystic fibrosis and Adult Respiratory Distress Syndrome (ARDS), Lung fibrosis, Sarcoidosis as well as in non-respiratory situations like Erectile dysfunction [31].

It is available as both intravenous as well as inhalational preparations. The half-life of the drug is 1-2 mins and the apparent volume of distribution is 14ml/kg. This drug is almost eliminated by the renal route where 35% elimination occurs in the first 4 hrs and 90% occurs within 24 hrs. It has no significant clinical drug-drug interactions and insufficient data is available on its use in pregnancy and lactation. Intravenous administration is associated with side effects like tachycardia, flushing, hypotension, diarrhea, and alterations in ECG (bigeminy) [32].

Patients suffering from Pulmonary Arterial Hypertension (PAH) were successfully treated with inhaled Aviptadil which caused a reduction in pulmonary artery pressure as well as improvement in cardiac output and mixed venous oxygen concentration [33].

Table 1. Effect of VIP on various experimental animal models of acute lung injury

Animal Models Tested for	Etiopathology of Lung Injury	References
Rat	NDMD induced lung injury w/ arginine	Said 1996, Said & Dickman 2000
Rat	Xanthine/xanthine oxidase-induced lung injury in perfused lungs	Berisha 1990, Misra 1990
Guinea Pig	Paraquat (methyl viologen)	Pakbaz 1993, Said & Dickman 2000
Rat	Hydrochloric acid induced pulmonary edema	Foda 1988
Sheep	Intravenous infusion of platelet-activating factor	Pakbaz 1988
Dog	Intravenous infusion of platelet-activating factor	Pakbaz 1988
Guinea Pig	Phospholipase C	Pakbaz 1991
Rat	Cobra venom factor model of septic shock	Mulligan 1992

In another open level phase, 2 clinical study 20 patients suffering from histologically proven sarcoidosis was treated with inhaled Aviptadil for 4 weeks which causes a significant reduction of TNF-Alpha and increment of CD4+CD127−CD25+ T cells in their bronchoalveolar lavage fluid [34]. Safety evaluation of Aviptadil was performed by conducting five Phase 2 trials under the observation of European regulatory authority EMA and Aviptadil was found to be a well-tolerated drug with fewer side effects like hypotension, flushing, diarrhea. Another open-label phase 1 study was conducted in 2005 among 8 patients suffering from sepsis-related ARDS (all were on mechanical ventilation) who have treated with intravenous Aviptadil infusion over 12 hrs at the dose of 50-100 pmol/kg/hr. Seven among those eight critically ill patients were successfully taken out of the ventilator and discharged home uneventfully; apart from that no drug-related serious adverse event was recorded and serial estimation of serum blood TNF-Alpha level showed significant decrement at the end of the treatment [35].

Role play by Aviptadil in COVID 19

SARS COV 2 infection is characterized by the hyperimmune response and dysregulated productions of cytokines and chemokines which play a pivotal role in severe lung injury and unfavorable clinical outcomes of patients suffering from COVID 19 disease [36-39].

Several nonstructural proteins (nsp) play a significant role in SARS COV2 viral RNA replication process. Among them, the SARS COV2 nsp6-nsp 10 complex works as a 2′-O- methyltransferase (MTase) [40]. This complex is also necessary to evade the immune recognition process [41]. Results of In silico structural bioinformatics analyses have demonstrated the potential sites of binding specificity between Aviptadil and nsp 16. The interaction model also showed the process of initial binding of Aviptadil with nsp10 & nsp 16 which may inhibit the 2 -O-MTase activity of the SARS-CoV nsp10/16 complex [42]. The SARS-CoV2 virus enters the ATII cell through the binding of its spike protein to Angiotensin-Converting Enzyme 2 (ACE2) surface receptors [43]. Unlike the AT I cells, only ATII cells express the VPAC1 receptor to which VIP binds with, thus VIP and its analogs deserve special attention as a therapeutic option to combat the hypoxemic lung injury in COVID 19.

Aviptadil is the only pulmonary therapeutic agent to have been granted Fast Track status by the US FDA and to be allowed into both phase 2/3 clinical trials, as well as an expanded use protocol for those who are unable to enter the clinical trial because of excluded comorbidity.

The initial use of Aviptadil via intravenous route for the first time (after getting the authorization of emergency use IND from FDA) was reported in a case report by Jihad Georges Youssef et al when a double lung transplant patient (additionally in a stage of antibody-mediated rejection got infected with SARS COV2 and subsequently developed severe respiratory failure) was treated by Aviptadil at Houston Methodist Hospital. After the third dose of Aviptadil via infusion there was a dramatic improvement in oxygen saturation and radiographic changes which ultimately lead to getting the patient discharged from the hospital and was alive till 28 days after post-discharge as per the latest information gathered from the study [44]. In another case series of twenty-one consecutive lab-confirmed SARS COV-2 patients with multiple comorbidities after being treated with Intravenous Aviptadil showed significant improvement both from the radiological as well as a clinical point of view because most of them were sent back to home after weaning from mechanical ventilation as well as decannulated from ECMO support which was also associated with biochemical improvements in the form of the steady decline of inflammatory markers (eg IL6 & CRP) [45].

Currently, nine clinical trials are on the list (two of them in India), where Aviptadil is being tried via both the inhalational and intravenous route and tested subsequently based on some outcome parameters to assess the safety and efficacy of the drug in comparison to the use of placebo/ Remdesivir/ Monoclonal antibody and other immunosuppressants in treatment of COVID 19 disease complicated by severe respiratory failure. The details of those trials are summarized in Table 2. Among those 9 trials, 7 of them are in the recruitment stage comprising the trial with maximum sample size, where one trial is completed and the data of the remaining one is available recently.

Among all the trials mentioned in Table 2, the only trial that has been completed recently on February 2021 demonstrated promising results on the intravenous use of Aviptadil in COVID-19. In this multicenter, placebo-controlled trial 196

patients with COVID-19 respiratory failure were randomized 2:1 to receive 3 days of intravenous aviptadil or placebo. The primary endpoint was "alive and free from respiratory failure at day 60." The investigators also studied the mechanistic effect of aviptadil on blocking cytokine production and its linkage to survival and recovery from respiratory failure. It was found that when controlling for baseline severity and site of care, patients treated with aviptadil were significantly more likely to be alive and free from respiratory failure at 60 days, compared to those treated

with placebo (P=.02) and demonstrated significance on numerous other clinical endpoints. Without controlling for the site of care, a two-fold increased odds of survival was seen at 60 days (95% CI 1.0 – 3.9; P=.035). Biomarker analysis demonstrates that aviptadil significantly decreased the probability of an IL-6 increase relative to placebo (50% vs. 71%; p=.04) and that preventing this cytokine rise was highly correlated with survival and recovery (P<.0001) regardless of baseline severity or treatment site [46].

Table 2. Summary of Current Trials on Aviptadil in COVID 19

No	Study Title	Drugs used	Location	Recruitment Status	Trial Identifier No	Estimated Sample Size
1	A Comparative, Multicenter, Placebo-Controlled, Double-Blind Phase II Clinical Trial Evaluating the Efficacy, Safety and Tolerability of Inhaled Aviptadil in Patients With COVID-19 Pulmonary Involvement - HOPE	Aviptadil Placebo	Turkey	Recruiting	NCT04844580	80
2	Inhaled Aviptadil for the Treatment of COVID-19 in Patients at High Risk for ARDS: A Randomized, Placebo Controlled, Multicenter Trial	Aviptadil Placebo	Switzerland	Recruiting	NCT04536350	82
3	Inhaled ZYESAMI™ for the Treatment of Severe COVID-19	Aviptadil Placebo	United States	Recruiting	NCT04360096	144
4	A Multicenter, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients With Acute Respiratory Distress Syndrome Associated With COVID-19	Aviptadil Remdesivir Placebo	United States	Recruiting	NCT04843761	640
5	I-SPY COVID TRIAL: An Adaptive Platform Trial to Reduce Mortality and Ventilator Requirements for Critically Ill Patients	Aviptadil Remdesivir Pulmozyme Celecoxib Famotidine Narsoplimab Cyclosporine IC14	United States	Recruiting	NCT04488081	1500
6	ZYESAMI (Aviptadil) for the Treatment of Critical COVID-19 With Respiratory Failure	Aviptadil Placebo	United States	Completed	NCT04311697	196
7	ZYESAMI (Aviptadil) Intermediate Population Expanded Access Protocol	Aviptadil	United States	Avialable	NCT04453839	196
8	A Randomized, Double blind, Placebo controlled Multi-centric, Phase III Clinical Trial to Evaluate the Efficacy and Safety of Aviptadil for Injection 500 mcg/vial in Treatment of Subjects Hospitalized with Respiratory failure/acute respiratory distress syndrome associated with severe Coronavirus Disease (COVID-19)	Aviptadil Placebo	India	Recruiting	CTRI/2021/04/033118	150
9	A Randomized, Double blind, Placebo controlled Multi-centric, Phase III Clinical Trial to Evaluate the Efficacy and Safety of Aviptadil for Injection 500 mcg/vial in Treatment of Subjects Hospitalized with Respiratory failure/acute respiratory distress syndrome associated with severe Coronavirus Disease (COVID-19)	Aviptadil Placebo	India	Recruiting	CTRI/2021/06/034373	152

As the study is limited by its insufficient power and other important outcome analysis and 60 days endpoint assessment reports are still awaited it will be too earlier to conclude about the study objective of this trial. But it is also true that as per the available data about the use of this molecule in ARDS related to sepsis as well as used in the preclinical lung injury model are concerned this molecule retains the hope to become an effective treatment option in the management of respiratory failure caused by SARS COV-2 infection.

Conclusion

Aviptadil, as a synthetic VIP holds a promising place in the armamentarium of treatment of SARS COV-2. Class effect of this drug is already established in the almost similar clinical scenario of ARDS caused by sepsis as well as other related lung injuries in preclinical models. The safety data of this molecule has also a favorable notation on the use in several respiratory airway diseases. Current interim analysis data about the safety and efficacy of this molecule is encouraging despite limitations regarding the sample

size of the study affecting the power. Upcoming results from the ongoing clinical trials will play a pivotal role in treatment policy-making aspects. More robust data on a larger target population will be immensely helpful to prove its impact on the reduction of the disease burden in the treatment of this deadly virus.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

References

1. Chacko J, Unais M. Pharmacologic treatment of COVID-19: Evidence-based update. Indian J Respir Care. 2021;10,Suppl S1:34-8

2. Heustess AM, Allard MA, Thompson DK, et al. Clinical management of COVID-19: A Review of pharmacological treatment options. Pharmaceuticals. 2021;14:520.

3. Said SI, Mutt V. Potent peripheral and splanchnic vasodilator peptide from normal gut. Nature.1970;225:863-4.

4. Li L, Hua S, Yue S, et al. Vasoactive intestinal polypeptide induces surfactant protein A expression in ATII cells through activation of PKC/c-Fos pathway. Peptides. 2010;31:2016-51.

5. Mossel EC, Wang J, Jeffers S, et al. SARS-CoV replicates in primary human alveolar type II cell cultures but not in type I-like cells. Virology. 2008;372:127-35.

6. Tang H, Welton A, Ganea D. Neuropeptide regulation of cytokine expression: Effects of VIP and RO 25-1553. J Interferon Cytokine Res. 1995;15:993-1003.

7. Voice JK, Grinninger C, Kong Y, et al. Roles of vasoactive intestinal peptide (VIP) in the expression of different immune phenotypes by wild-type mice and T cell targeted type II VIP receptor transgenic mice. J Immunol. 2003;170:308-14.

8. Gonzalez-Rey E, Delgado M. Vasoactive intestinal peptide and regulatory T-cell induction: a new mechanism and therapeutic potential for immune homeostasis. Trends Mol Med. 2007;13:241-51.

9. Delgado, Mario Martínez, Carmen Pozo, David et al. Vasoactive Intestinal Peptide (VIP) and Pituitary Adenylate Cyclase-Activation Polypeptide (PACAP) Protect Mice from Lethal Endotoxemia Through the Inhibition of TNF-α and IL-6. J Immunol. 1999;162:1200-5.

10. Berisha HI, Bratut M, Bangale Y, et al. New evidence for transmitter role of VIP in the airways: Impaired relaxation by a catalytic antibody. PulmPharmacolTher. 2002;15:121-7.

11. Sharma V, Delgado M, Ganea D. Granzyme B, a new player in activation-induced cell death is downregulated by vasoactive intestinal peptide in Th2 but not Th1 effectors J Immunol. 2005;176:97–110.

12. Said SI. Vasoactive intestinal peptide in the lung. Ann N Y Acad Sci. 1988;527:450-64.

13. Hasaneen NA, Foda HD, Said SI. Nitric oxide and vasoactive intestinal peptide as co-transmitters of airway smooth-muscle relaxation: analysis in neuronal nitric oxide synthase knockout mice. Chest. 2003;124:1067-72.

14. Saga T, Said SI. Vasoactive intestinal peptide relaxes isolated strips of human bronchus, pulmonary artery, and lung parenchyma. Trans Assoc Am Physicians. 1984;97:304-10.

15. Nagahiro I, Yano M, Boasquevisque CH, et al. Vasoactive intestinal peptide ameliorates reperfusion injury in rat lung transplantation J. Heart Lungn Transplant. 1998;17:617-21.

16. Virgolini, A Kurtaran, M Raderer. Vasoactive intestinal peptide receptor scintigraphy. J Nucl Med. 1995;36:1732–9.

17. Mathioudakis A, Chatzimavridou-Grigoriadou V, Evangelopoulou E, et al. Vasoactive intestinal Peptide inhaled agonists: potential role in respiratory therapeutics. Hippokratia. 2013;17:12-6.

18. Virgolini I, Kurtaran A, Raderer M, et al. Vasoactive intestinal peptide receptor scintigraphy. J Nucl Med. 1995 36:1732-9.

19. H Pakbaz, H Berisha, H Sharaf, et al. VIP enhances and nitric oxide synthaseinhibitor reduces survival of rat lungs perfused ex vivo. Ann N Y Acad Sci. 1994;723:426-8.

20. Li L, She H, Yue SJ, et al. Role of c-fos gene in vasoactive intestinal peptide promoted synthesis of pulmonary surfactant phospholipids. RegulPept. 2007 3;140:117-24.

21. Delgado M, Munoz-Elias EJ, Kan Y, et al. Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide inhibit tumor necrosis factor alpha transcriptional activation by regulating nuclear factor-kB and cAMP response element-binding protein/c-Jun J. Biol. Chem. 1998;273:31427–36.

22. Mason R J. Pathogenesis of COVID-19 from a cell biology perspective. Eur Respir J. 2020;55:2000607.

23. Onoue S, Ohmori Y, Endo K, et al. Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide attenuate the cigarette smoke extract-induced apoptotic death of rat alveolar L2 cells. Eur. J. Biochem. 2004;271:1757-67.

24. Temerozo, Jairo & Sacramento, Carolina & Fintelman-Rodrigues, Natalia & Pao, et al. The neuropeptides VIP and PACAP inhibit SARS-CoV-2 replication in monocytes and lung epithelial cells and decrease the production of proinflammatory cytokines in infected cells.

25. Li L, Luo ZQ, Zhou, et al. Effect of vasoactive intestinal peptide on pulmonary surfactants phospholipid synthesis in lung explants. Acta Pharmacol Sin. 2004;25:1652-8.

26. Li L, Hua S, Yue S, et al. Vasoactive intestinal polypeptide induces surfactant protein A expression in ATII cells through activation of PKC/c-Fos pathway. Peptides. 2010;31:2016-51.

27. Mathioudakis AG, Chatzimavridou-Grigoriadou V, Evangelopoulou E, et al. Vasoactive intestinal peptide inhaled agonists: potential role in respiratory therapeutics. Hippokratia. 2013;17:12-6.

28. Delgado M, Martinez C, Pozo D, et al. Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activation polypeptide (PACAP) protect mice from lethal endotoxemia through the inhibition of TNF-alpha and IL-6. J Immunol. 1999;162:1200-5.

29. Delgado M, Munoz-Elias EJ, Kan Y, et al. Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide inhibit tumor necrosis factor alpha transcriptional activation by regulating nuclear factor-kB and cAMP response element-binding protein/c-Jun J Biol Chem. 1998;273:31427-36.

30. Hashimoto S, Kobayashi A, Kooguchi K, et. al. Upregulation of two death pathways of perforin/granzyme and FasL/Fas in septic acute respiratory distress syndrome. Am J Respir Crit Care Med. 2000,161:237-43.

31. Sharma V, Delgado M, Ganea D. Granzyme B, a new player in activation-induced cell death is downregulated by vasoactive intestinal peptide in Th2 but not Th1 effectors. J Immunol. 2006;176:97-110.

32. Jonathan C. Javitt, MD, MPH. Perspective: The Potential Role of Vasoactive Intestinal Peptide in treating COVID-19. Authorea. May 13, 2020.

33. Raveendran AV, dhuhli AL, Khalid Salim, Kumar HG. Role of Aviptadil in COVID-19. BMH Medical J. 2021;8:77-83.

34. Leuchte HH, Baezner C, Baumgartner RA, et al. Inhalation of vasoactive intestinal peptide in pulmonary hypertension. Eur Respir J. 2008;32:1289–94.

35. Prasse A, Zissel G, Lützen N, et al. Inhaled vasoactive intestinal peptide exerts immunoregulatory effects in sarcoidosis. Am J RespirCrit Care Med. 2010 15;182:540-8.

36. Youssef, Jihad G and Said, Sami and Youssef, George and Javitt, Matthew J. and Javitt, Jonathan, Treatment of Sepsis-related Acute Respiratory Distress Syndrome with Vasoactive Intestinal Peptide Available at SSRN: https://ssrn.com/abstract=3662952 access date July 29, 2020.

37. Chen G, Wu D, Guo, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest. 2020;130:2620–9.

38. Tang D, Comish P, Kang R. The hallmarks of COVID-19 disease. PLoS Pathogens. 2020;16:e1008536.

39. Ragab D, Salah Eldin H, Taeimah M, et al. The COVID-19 Cytokine Storm; What We Know So Far. Front. Immunol. 2020;16;11:1446.

40. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, et al. Complex Immune

Dysregulation in COVID-19 Patients with Severe Respiratory Failure. Cell Host Microbe. 2020;27:992-1000.

41. Bouvet M, Debarnot C, Imbert I, et al. In vitro reconstitution of SARS-coronavirus mRNA cap methylation. PLoSPathog. 2010;6:e1000863.

42. Bollati M, Milani M, Mastrangelo E, et al. Recognition of RNA cap in the Wesselsbron virus NS5 methyltransferase domain: implications for RNA-capping mechanisms in Flavivirus. J Mol Biol. 2009;385:140-52.

43. Sultan F. Alnomasy, Bader S. Alotaibi, Ziyad M. Aldosari et al. Inhibitory effects of aviptadil on the SARS-CoV-2 nsp10/ nsp16 protein complex. Research Square. 2021

44. Mason RJ. Pathogenesis of COVID-19 from a cell biology perspective. Eur Respir J. 2020;55:2000607.

45. Youssef JG, Zahiruddin F, Al-Saadi M, et al. Brief report: rapid clinical recovery from critical COVID-19 with respiratory failure in a lung transplant patient treated with intravenous vasoactive intestinal peptide. Preprints 2020;2020070178.

46. Youssef JG, Lee R, Javitt J, et al. Intravenous Aviptadil Is Associated with Increased Recovery and Survival in Patients with COVID-19 Respiratory Failure: Results of a 60-Day Randomized Controlled Trial. SSRN. Critical Care Exploration. 2021;4:e0607.