Review Article

Aviptadil- Class Effect of a Synthetic Vasoactive Intestinal Peptide as a Treatment Option in COVID-19 Patients with Severe Respiratory Failure

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Abstract

The whole world has witnessed an unimaginable, unforgettable medical disaster in the last 1 and ½ years in form of the demise of innumerable people due to the current pandemic of SARS COV-2. Despite several efforts to develop strong evidence-based effective and safe treatment regimens, the options remain very limited, to date. Vasoactive intestinal peptide (VIP) discovered as a gut peptide hormone in earlier days was found to have diversified physiological action with specific features of lung protection-related activities. It has a unique feature of binding to angiotensin-converting enzyme (ACE) receptor of Type II alveolar cell to which the COVID 19 virus also binds. Aviptadil as a synthetic VIP has already been proved to be an effective option in the treatment of severe respiratory failure 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 currently, ongoing trials will clarify the class effect of this drug in the treatment of COVID 19 in the days to come.

Keywords: Interim, pandemic, SARS COV-2, synthetic, vasoactive intestinal peptide

Introduction

COVID 19 has created an unprecedented situation globally over the last 18 months. Till July 19, 2021, almost 189,921,964 confirmed cases of COVID-19, including 4,088,281 deaths, were reported to the WHO all over the world, and the death toll continues to increase every day. This pandemic has led 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 such as 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/noninvasive 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 combating fatal complications such as 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 held initially as the recent randomized controlled trials failed to demonstrate any added benefit with regard to the mortality and morbidity reports of the disease. Cytokine inhibitors such as Tocilizumab and other immunomodulatory drugs need further evaluation among a larger participating population of clinical trials to establish their efficacy.[1]

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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 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 gastrointestinal 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, B- and T-lymphocytes.[4,5]

Physiological role in the respiratory system: 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 vasoactive intestinal peptide receptor type 1 and 2 (VPAC 1 and 2). These receptors are also activated by Pituitary Adenylate Cyclase Activating Polypeptide which belongs to the same family as VIP. VPAC 1 receptor is predominantly located in the 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] AT-II cells despite comprising only 5% of total lung tissue play an important role in surfactant production that 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] In addition, 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 nonadrenergic-noncholinergic bronchodilatation which is 100 times more potent than isoproterenol as well as 50 times more potent vasodilator 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. They include positive chronotropic, inotropic, and coronary vasodilatory actions, secretion of water and electrolytes from the intestinal lumen, pancreatic juice, and bile, stimulation of pepsinogen secretion, regulation of prolactin secretion, and promoting vaginal lubrication. It inhibits T lymphocyte proliferation,[16] promoting T-helper 2 lymphocytes differentiation against T-helper lymphocytes, and regulatory T-cell (T regs) induction.[16,17] It downregulates several macrophage-mediated inflammatory cytokines and proinflammatory receptors.[18] It plays a role of an inhibitory neurotransmitter of the nonadrenergic, noncholinergic autonomic nervous system.[19] It inhibits the synthesis as well as activation of NF-KB which blocks the process of tumor necrosis factor (TNF) alpha generation.[20]

Pathophysiological Basis of Use of Vasoactive Intestinal Peptide 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.[21] AT-II cells express VPAC 1 receptors on its surfaces to which the VIP binds and prevents the process of apoptosis in lung injury.[22] 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.

VIP has demonstrated its beneficial effects on lung injury in several animal models [Table 1]. Unlike the anti- interleukin (IL) 6 drugs, it preserves the surfactant production as well as protects the Type II alveolar cells of the lung.[4,17,23] Other than the surfactant producing and anti-inflammatory activity, VIP has the property of potentially inhibiting the Fos ligand expression and thereby halting the progression of Fas ligand-mediated cell death.[9,21] 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.[24] As a proven inhibitor of granzyme and perforin, VIP plays an important role in the prevention of cell death in lung tissue.[11]

Aviptadil and its 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 the Food and Drug Administration (FDA) to treat respiratory airway diseases such as asthma, chronic obstructive airway disease, cystic fibrosis, pulmonary hypertension, adult respiratory distress syndrome (ARDS), lung fibrosis, sarcoidosis as well as in nonrespiratory situations such as erectile dysfunction.[25]

It is available as both intravenous as well as inhalational preparations. The half-life of the drug is 1–2 min and the apparent volume of distribution is 14 ml/kg. This drug is almost eliminated by the renal route where 35% elimination occurs in the first 4 h and 90% occurs within 24 h. It has no significant clinical drug–drug interactions and insufficient

Table 1: Effect of vasoactive intestinal peptide 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 and Dickman 2000
Rat	Xanthine/xanthine oxidase-induced lung injury in perfused lungs	Berisha 1990, Misra 1990
Guinea pig	Paraquat (methyl viologen)	Pakbaz 1993, Said and 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

NDMD: N-Dimethyl Daunomycin

data is available on its use in pregnancy and lactation. Intravenous administration is associated with side effects such as tachycardia, flushing, hypotension, diarrhea, and alterations in electrocardiogram (bigeminy).[26]

Patients suffering from pulmonary arterial hypertension were successfully treated with inhaled Aviptadil which caused a reduction in pulmonary artery pressure, improvement in cardiac output, and mixed venous oxygen concentration.[27] In another open-label phase 2 clinical study, 20 patients suffering from histologically proven sarcoidosis were 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.[28] Safety evaluation of Aviptadil was performed by conducting five Phase 2 trials under the observation of the European regulatory authority. Aviptadil was found to be a well-tolerated drug with fewer side effects such as hypotension, flushing, diarrhea. Another open-label phase 1 study was conducted in 2005 among eight patients suffering from sepsis-related ARDS all were on mechanical ventilation). They were treated with intravenous Aviptadil infusion over 12 h at the dose of 50–100 pmol/kg/h. Seven among those eight critically ill patients were successfully taken out of the ventilator and discharged home uneventfully. Furthermore, 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.[29]

Use 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.[30-33]

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).[34] This complex is also necessary to evade the immune recognition process.[35] 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 and nsp 16 which may inhibit the 2-O-MTase activity of the SARS-CoV nsp10/16 complex.[36] The SARS-CoV2 virus enters the ATII cell through the binding of its spike protein to angiotensin-converting enzyme 2 (ACE2) surface receptors.[22] Unlike the AT I cells, only ATII cells express the VPAC1 receptor to which VIP binds. 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 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 led to recovery, getting the patient discharged from the hospital and was alive till 28 days after postdischarge as per the latest information gathered from the study.[37] In another case series of twenty-one consecutive lab-confirmed SARS COV-2 patients with multiple comorbidities, patients showed significant radiological and clinical improvement after being treated with intravenous Aviptadil. Most of them were sent back home after weaning from mechanical ventilation, decannulation from extracorporeal membrane oxygenation support. It was also associated with biochemical improvement in the form of steady decline of inflammatory markers (e.g., IL6 and C-reactive protein).[38]

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 with 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

Table 2: Summary of current trials on Aviptadil in corona virus disease-2019

Number	Study title	Drugs used	Location	Recruitment status	Trial identifier number	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 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 COVID-19	Aviptadil Placebo	India	Recruiting	CTRI/2021/06/034373	152

COVID-19: Corona virus disease-2019, ARDS: Adult respiratory distress syndrome, I-SPY COVID: Investigation of serial studies to predict your COVID

with maximum sample size, where one trial is completed and the data of the remaining one has been made available recently.

An interim analysis report of that completed trial has come into the limelight recently. In that study, multi-centered randomized double-blind placebo-controlled Phase 2b/3a trial safety and efficacy of intravenous Aviptadil was compared with placebo among severe symptomatic COVID 19 patients with features of respiratory failure with 28-day and 60-day endpoint. Among the finally recruited 196 study participants, 131 patients received 3 successive doses of 12-hour intravenous infusions of Aviptadil at 50/100/150 pmol/kg/h and a significant percentage of those Aviptadil arm patients recovered and went back home as well as meeting the endpoint of 28 days survival and statistically significant difference of 10 days reduction of hospital stay were noted.[39] As the study is limited by its insufficient power and other important outcome analysis and for 60 days endpoint assessment reports are still awaited, it will be too earlier to conclude about the study objective of this trial. 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 also have a favorable notation on its use in several respiratory airway diseases. Current interim analysis data about the safety and efficacy of this molecule are encouraging in spite of 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.

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Conflicts of interest

There are no conflicts of interest.

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