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Medicine in Drug Discovery 6 (2020) 100042

Contents lists available at ScienceDirect

Medicine in Drug Discovery

journal homepage: https://www.journals.elsevier.com/medicine-in-drug-discovery

Review Article

Perspectives for the use of therapeutic Botulinum toxin as a multifaceted candidate drug to attenuate COVID-19

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ARTICLE INFO

Article history:
Received 20 April 2020
Received in revised form 22 April 2020
Accepted 24 April 2020
Available online 29 April 2020

Keywords:
COVID-19
Coronavirus
SARS-CoV-2
ACE2
Botulinum toxin
Botox

ABSTRACT

The recent outbreak of coronavirus disease (COVID-19) resulting from a distinctive severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) continues to evolve in many countries and pose life-threatening clinical issues to global public health. While the lungs are the primary target for the SARS-CoV-2-mediated pathological consequence, the virus appears to invade the brain and cause unpredicted neurological deficits. In the later stage, COVID-19 can progress to pneumonia, acute respiratory failure, neurodegeneration and multi-organ dysfunctions leading to death. Though a significant portion of individuals with COVID-19 has been recovering from clinical symptoms, the pathological impact of the SARS-CoV-2 infection on the structural and functional properties of the lungs, heart, brain and other organs at the post-recovery state remains unknown. Presently, there is an urgent need for a remedial measure to combat this devastating COVID-19. Botulinum toxins (BoNTs) are potent neurotoxins that can induce paralysis of muscle and acute respiratory arrest in humans. However, a mild dose of the purified form of BoNT has been known to attenuate chronic cough, dyspnoea, pneumonia, acute respiratory failure, abnormal circulation, cardiac defects and various neurological deficits that have been recognised as the prominent clinical symptoms of COVID-19. Considering the fact, this review article provides 1) an overview of the SARS-CoV-2 mediated pathological impact on the lungs, heart and brain, 2) signifies the therapeutic uses of BoNTs against pulmonary failure, cardiac arrest and neurological deficits, and 3) emphasize the rationality for the possible use of BoNT to prevent SARS-CoV-2 infection and manage COVID-19.

Contents

1. Introduction

The ongoing outburst of coronavirus disease-2019 (COVID-19) has rattled the entire human population as it potentiates the life-threatening acute medical complications and death worldwide. A distinctive coronavirus designated as severe acute respiratory syndrome (SARS)-CoV-2, has been determined to be accountable for the ongoing COVID-19 [1]. The SARS-CoV-2 responsible for COVID-19 in humans has been proposed to be originated in bats and pangolins [2]. The first incidence of the SARS-CoV-2 transmission from animal to humans has been known to have occurred in Wuhan, Hubei Province, China in late 2019 [3–5]. Since then, SARS-CoV-2 mediated COVID-19 continues to emerge all over the world through

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http://dx.doi.org/10.1016/j.medidd.2020.100042

person-to-person transmission of viral air droplets. The victims encountered by the SARS-CoV-2 have been reported to develop a wide range of clinical symptoms that include dry cough, sore throat, fever, body pain, headache, abdominal discomfort, diarrhoea and fatigue [4,5]. In the severe stage, SARS-CoV-2 infection has been known to cause pneumonia, acute respiratory failure, encephalopathy and multi-organ dysfunctions, thereby leading to death [4–6]. In general, coronaviruses have been known to cross the blood-brain barrier (BBB) and affect the central nervous system (CNS) [7]. A growing body of evidence suggests that the loss of smell and taste might be the distinct clinical signs of COVID-19 which provides a clue that the SARS-CoV-2 infection affects the sensory inputs and impairs the gustatory, and olfactory regions of the brain [8,9]. The SARS-CoV-2 mediated neuropathogenicity in the brain has been suggested to be responsible for the respiratory failure leading to death in subjects with COVID-19 [7,10]. Though a substantial portion of SARS-CoV-2 infected individuals has been recovering from the clinical symptoms, the pathological impact of the COVID-19 on the structural and functional properties of the lungs, heart, brain and other organs even after the recovery may not be excluded. While drug-based therapeutic interventions and establishment of vaccination against the COVID-19 are in rapid progress, the pathological impact of the SARS-CoV-2 infection on the brain that alters the neuroplasticity requires an intense scientific focus. Altogether, the unforeseen growing pathological stigma of COVID-19 has necessitated the need for the combined development of pharmacological, immunological, biochemical, genetic-based antiviral approaches as well as the anti-inflammatory and cytoprotective treatment regime that could safeguard the organs that are highly vulnerable during COVID-19. (See Fig. 1).

Botulinum toxins (BoNTs) are bacterial proteins that induce paralysis of muscle and sudden respiratory failure leading to death in humans [11,12]. However, a very mild dose of the purified forms of BoNT have been known to yield therapeutic benefits against many diseases including strabismus, blepharospasm, chronic migraine, overactive bladder and also used as an anti-ageing cosmetic agent [12,13]. Ample scientific evidence suggests that the therapeutic roles of BoNT have been extending as they provide relief from various forms of respiratory failures, cardiovascular defects and neurological deficits [11–17]. Notably, the aforementioned pathological complications have been reported as the clinical feature of COVID-19. Considering the fact, the benefit of therapeutic BoNT can be repurposed to ameliorate SARS-CoV-2 mediated various pathological effects including pulmonary failure, cardiovascular defects and neurological deficits noticed in cases with COVID-19. Thus, this review article provides 1) an overview of the SARS-CoV-2 mediated pathological impact on the lungs, heart and brain, 2) describes the therapeutic uses of BoNT against pulmonary failure, cardiovascular defects and neurological deficits, and 3) emphasize the rationality for the possible uses of BoNT to prevent SARS-CoV-2 infection and manage COVID-19 at various aspects.

2. The pathological impact of COVID-19 on the lungs, heart and brain

The SARS-CoV-2 belongs to a family of positive-strand RNA viruses of the genus Beta-coronavirus and it shares genetic similarity with two other viral strains that appear to have originated in bats [2,18]. The angiotensin-converting enzyme 2 (ACE2) has been recognized as one of the key receptors for the SARS-CoV-2 [19]. Thus, cells that express ACE2 are vulnerable to the infection and are considered as the main target of the SARS-CoV-2 [20,21]. The ACE2 gene is highly expressed in the respiratory tract and thus the lungs are the major hotspot of SARS-CoV-2 infection and its pathogenic events [22]. However, SARS-CoV-2 infection appears to takes place also in the gastrointestinal tract, cardiovascular system, brain and other organs that are known to express the ACE2 [19,20,23]. Individuals with diabetes, obesity, hypertension, and cardiovascular disorders have been recognised to be highly susceptible to SARS-CoV2 infection leading to the development of COVID-19 [1,6,24]. The abnormal expression and functions of the ACE2 have been linked to diabetes, obesity, hypertension, and cardiovascular disorders [4,20,25]. Moreover, recent findings suggest that the density of the ACE2 on the cells increases upon ageing and its expression has been found to be higher in men than women since SARS-CoV-2 appears to affect men than women in many countries [26]. While SARS-CoV-2 infection develops various clinical symptoms in the host, acute respiratory distress syndrome (ARDS) represents a pathological hallmark of COVID-19 [27]. In many cases, pneumonia appears to be the major clinical consequence of SARS-CoV-2 infection due to prominent proinflammatory processes in the alveoli of the lungs [2,26,27]. Many reports from in vivo and in vitro studies and histopathological findings on the post-mortem human lungs suggest that SARS-CoVs causes apoptosis in alveolar cells and degeneration of small blood vessels of the lungs [1,6,26–28]. In the intensive conditions, respiratory arrest has been a major cause of COVID-19 associated death [2,5,26]. In addition, the available clinical data suggest that a significant portion of COVID-19 patients have hypertension and cardiovascular disease [6,21,24,29]. The medications that are used to manage the symptoms of hypertension and cardiovascular disorders in association with diabetes have been known to induce the expression of ACE-2 [20,22,23]. Thus, it has been correlated that individuals with hypertension, diabetes, cardiovascular disorders are at high risk of being infected with SARS-CoV-2 and developing COVID-19 [24,29]. Recent reports on the blood parameters indicated the elevated levels of creatine kinase and lactate

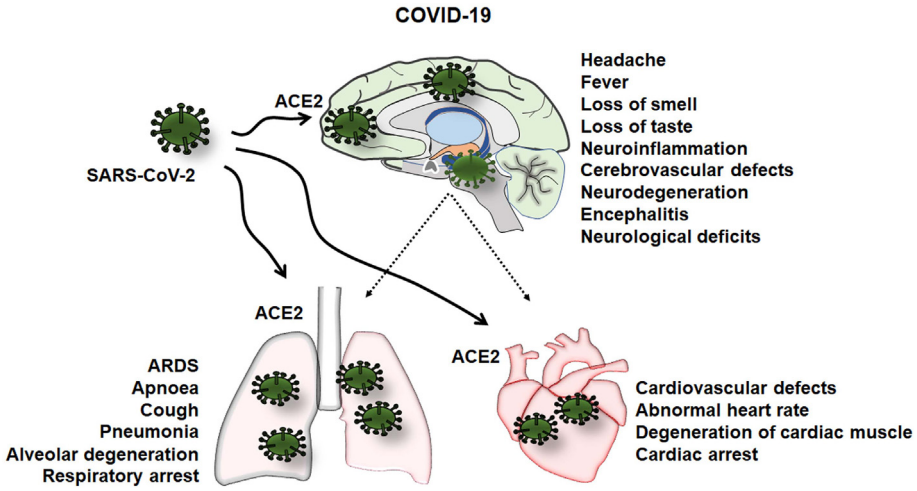

Fig. 1. Schematic representation of SARS-COVID-2 infection in the brain, lungs and heart that bears ACE2 expressing cells. The figure indicates the list of clinical symptoms of COVID-19 related to the brain, lungs and heart.

dehydrogenase in a significant proportion of individuals with COVID-19 [30,31]. The elevated levels of creatine kinase and lactate dehydrogenase in the circulation have been known to be the biomarkers of muscle degeneration and tissue damage in various organs including the heart and liver. Moreover, cardiac arrest has increasingly been noticed as one of the reasons for the mortality associated with COVID-19 [29,31] (Fig. 1).

Meanwhile, SARS-CoV-2 has been reported to enter into the brain leading to acute neuropathological signatures, while the expression of the ACE2 in the brain is evident [10,32]. Previous reports have clearly indicated that neural invasion of SARS-CoVs can be facilitated by olfactory neurons through nasal neuroepithelial cells [33,34]. The presence of the SARS-CoVs in cerebrospinal fluid (CSF) of infected individuals was also evident [35]. Upon the neural infection, the SARS-CoVs can elicit unregulatable neuroinflammatory responses, thereby leading to seizures, convulsions, loss of consciousness, encephalomyelitis and encephalitis [7,34,36,37]. Netland J. et al. reported that SARS-CoVs can invade the brain through the olfactory epithelium and can induce neuronal death in a transgenic mouse model that expresses the human ACE2 gene [38]. Though human subjects with autoimmune disorders like multiple sclerosis have been reported to be highly susceptible to get SARS-CoV2 infection, neurological abnormalities can increasingly be expected in the critical stage of any individuals with COVID-19 [39]. The viral infections mediated neuropathogenicity in the brain regions that regulate the respiratory, cardiac, gustatory and olfactory functions might be highly relevant for the COVID-19 cases (Fig. 1). In addition, COVID-19 may exhibit abnormal regulations of the hypothalamic pituitary adrenal (HPA) axis in association with panic, anxiety and depression-like disorders which may need an additional line of scientific focus. Considering the fact, the SARS-CoV-2 infection might impair the brain functions at the level of impaired synaptic plasticity, neuroinflammation, neurodegeneration and abnormal neurogenesis, gliosis leading to cognitive impairment and dementia similar to that of other neuro-invasive viruses including herpes simplex virus, poliovirus and HIV [40]. Moreover, the ACE2 gene expression and functions have been linked to the regulation of cerebral blood flow (CBF) in physiological state, while it can also be expected that SARS-CoV-2 infection can mediate abnormal turnover of the ACE2 gene leading to cerebrovascular defects [41]. Eventually, A recent study revealed that a significant portion of COVID-19 victims has been overlapped with signs of cerebrovascular disease [5,7,42]. Taken together, neuropathogenic correlates of SARS-CoV-2 mediated clinical symptoms in patients with COVID-19 requires an intensive assessment at various levels of neurological abnormalities. Meanwhile, implementation of a multifaceted drug that could yield beneficial effects against the clinical symptoms of COVID-19 needs to be designated; for which treatment option like therapeutic BoNTs might serve the purpose to combat COVID-19.

3. Clinical uses of botulinum toxins

BoNTs are considered as the most harmful biological substances currently known to humans [12,13]. BoNTs are mainly produced by strains of anaerobic spore-forming bacterium, *Clostridium botulinum*, [11,43]. Seven major serotypes of BoNTs have been characterized and designated as type A to G [44]. Among them, BoNT types A, B, E and F have directly been linked to induce lethal human diseases [11,12]. Structurally, BoNTs consist of a heavy and a light polypeptide chains of about 100 and 50 kDa in size respectively, coupled by a disulfide bridge [11,12]. The heavy chain of BoNT binds to its receptors at the presynaptic terminals of the cholinergic neurons and enters into the cytoplasm of the neurons as receptor-mediated endocytosis, where the disulfide bond between two polypeptide chains of BoNTs disassociates and gains their activated form [11,12]. The light chain binds to inactivate the proteins like synaptosomal-associated protein (SNAP)-25, vesicle-associated membrane protein (VAMP) and syntaxin that are responsible for the fusion of neurotransmitter containing vesicles with the lipid bilayer in the synaptic cleft, thereby preventing the release of acetylcholine (ACh) in cholinergic, parasympathetic and postganglionic sympathetic nerve endings. BoNT-mediated blockades of the ACh release and subsequent arrest in the cholinergic signalling pathway at the synaptic junctions have been regarded to cause dreadful muscle paralysis and death [11,12]. BoNTs are known to induce symptoms like dryness of the mouth and eyes, urinary retention, fluctuations of the blood pressure, abnormal heart beats, fatigue and dyspnoea [11–14,45]. The lungs are the primary target organ when BoNTs are inhaled as it induces acute pneumonitis and paralysis of breathing muscle leading to respiratory arrest [11–13,45]. However, a mild dose of the purified form of BoNT has been identified as a remarkable treatment measure against many human disease [11–13]. Notably, therapeutic BoNT has been implemented to reduce the severity of many disease and provide a cure to clinical conditions that include hyperhidrosis, chronic migraine, strabismus, hemifacial spasms, blepharospasm, abnormal heart rate, dysphagia and urinary bladder dysfunctions [11–13,17,45]. Moreover, a mild therapeutic dose of BoNT has clearly been shown to provide a beneficial effect against the clinical conditions with obstruction of the lung functions like chronic cough, bronchitis, asthma and dyspnoea [11,12,14,16,17,46] (Fig. 2).

Besides, therapeutic BoNTs are implemented to attenuate a number of neurological deficits which exhibit characteristics of different forms of movement disorders and cerebral palsy [11–13]. Notably, therapeutic BoNTs have clinically been utilized to control the abnormal movement disorders noticed in dystonia, Huntington's disease (HD), spinocerebellar ataxia (SCA), amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), spasticity from stroke and different types of Tic disorders [11–13,47]. Though the causative factors and clinical symptoms of the aforementioned disorders are highly

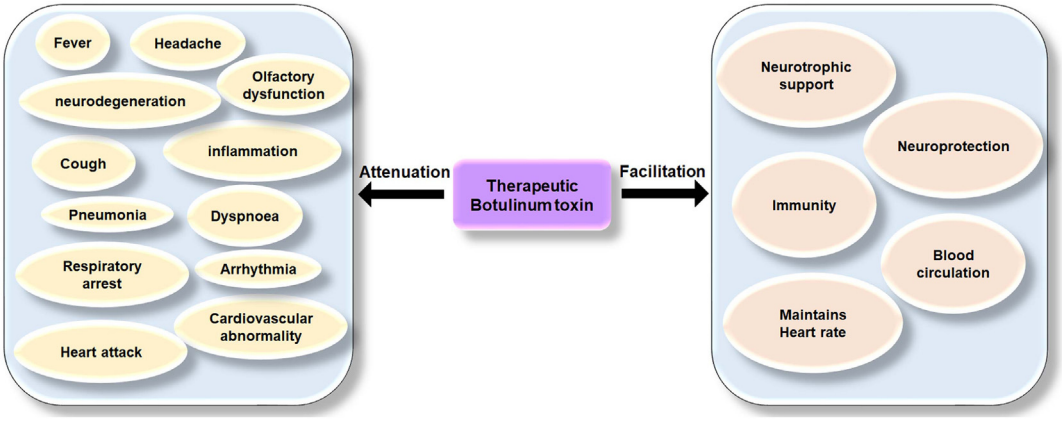

Fig. 2. An overview on the clinical use of therapeutic botulinum toxin to attenuate COVID-19.

dissimilar, therapeutic BoNTs appear to yield beneficial effects regardless of aetiological differences. Taken together, insight into the potential molecular targets of therapeutic BoNTs would be of great help to extend its curative potential to combat the refractory ongoing human diseases (Fig. 2).

4. Proposed scientific basis for the repurposing of botulinum toxin to combat COVID-19

Thus far, SARS-CoV-2 induced ARDS responsible for pneumonia and respiratory arrest has been implicated as a key determining factor for the extending casualties of the COVID-19 worldwide [4–6,10,27,31]. Meanwhile, cardiac arrest resulting from the SARS-CoV-2 infections has also been linked to mortality in individuals with COVID-19 [24]. Besides, SARS-CoV-2 appears to enter the CNS and elicit the neuropathogenicity in various brain regions that control body temperature, respiration and heart beat [10]. Experimental evidence derived from the tissue samples of both COVID-19 patients and the relevant animal models have strongly indicated that SARS-CoV-2 can also induce neuropathological outcomes like other neuro-invasive viruses [8,10,34,42,48]. Owing to the aforementioned fact, Li YC and co-workers have recently reported that COVID-19 patients exhibit many neurological problems and further indicated that the brainstem is highly vulnerable [10]. Moreover, the computerized tomography (CT) and magnetic resonance imaging (MRI) based findings revealed that the thalamus, medial temporal lobes and subinsular region are affected and development of encephalopathy is apparently evident in the brain of a subject with COVID-19 [49]. Considering the fact, it can be expected that individuals who have recovered from COVID-19 are at high risk of the onset of neurological, motor, cognitive deficits and psychiatric symptoms. Therefore, in addition to aiming the druggable strategies at peripheral and systemic levels, the brain represents one of the major therapeutic targets to manage the symptoms and evade COVID-19 related mortalities. Though inhibition of the expression and functions of the ACE2 gene using pharmacological inhibitors may be of help in prevention, it would not yield an ultimate cure for positive cases with COVID-19 [50]. Apart from the vaccination based preventive medical interventions against SARS-CoV-2 infection a number of disease-modifying strategies should be considered in order to manage and provide effectual defence, and recovery against COVID-19, as follows 1) reduction of the circulating viral load by pharmacological, biochemical and genetic interference-based anti-viral therapies along with multivitamins and nutrients to boost immunity against SARS-CoV-2 in positive cases, followed by 2) assigning anti-inflammatory treatment regimes to reduce the SARS-CoV-2 mediated chronic proinflammatory responses, 3) supplementation of antioxidants and cytoprotective agents, and 4) implementation of neurotrophic support to sustain the neuroplasticity. While many drugs can individually meet any one of the aforementioned strategies, identification of a single drug or establishment of a strategy with multipurpose therapeutic potentials might be highly appropriate for the moment.

The therapeutic forms of BoNT have been approved by the Food and Drug Administration (FDA) for the treatment of many clinical conditions including chronic headache and dystonia [11–13]. Besides, BoNTs have been licensed for its use as anti-ageing cosmetics [12,13,51]. In particular, mild therapeutic BoNT injection has been proven to be beneficial against migraine, body pain, persistent fever, chronic cough, pneumonia and dyspnoea [11–14,16,17,46], while those medical conditions are considered as the general clinical symptoms of COVID-19 [3–6,21,26,27,30,42,48,49]. Notably, a significant portion of patients with COVID-19 has been reported to exhibit lymphopenia, a clinical condition of having a low level of lymphocytes in the blood [52]. Therapeutic BoNT injections appear to elevate immune cell counts including increased platelet counts in the blood which might help fight the SARS-CoV-2 as it can enhance the antigen presentation and the macrophages-mediated phagocytosis to eliminate the virulent factors [53,54]. Moreover, therapeutic BoNT has been known to avert the irregular heart rhythm even after open heart surgery [55]. Therapeutic BoNT injection has been reported to improve blood circulation and oxygen supply thereby improving the survival rate of subjects with ischemic conditions [12,56–58]. Besides, implementation of therapeutic BoNT is an eminent clinical practice to manage movement disorders in a wide range of neurological deficits [11–13]. Remarkably, therapeutic BoNT appear to provide neuroprotection against cerebral ischaemic insults [59]. Eventually, the existing list of diseases treated by therapeutic BoNT are associated with increased levels of ACE2 in the respective organs or in the circulation. For example, abnormal expression levels of ACE2 have been recognized as a biomarker as well as a potential therapeutic target for chronic headache, dyspnoea, bronchitis, cardiovascular disorders, hypertension, neuroinflammation and neurological disorders [60–64]. While the underlying mechanisms of therapeutic BoNT on the recovery of the aforementioned clinical complications remains unclear, therapeutic BoNT can be proposed to suppress the expression of ACE2 [37,58]. Taken together, therapeutic BoNTs may also be used as a preventive measure against SARS-CoV-2 infection in population at risk (Fig. 2).

Recently, rigorous implementation of many drugs and therapeutic strategies has been envisaged against COVID-19. While the prediction of the clinical outcome of the proposed drugs and therapies are the major focus, the underlying mode of action and possible adverse effects associated with such therapeutic approaches may not be excluded. For example, hydroxychloroquine along with azithromycin has been proposed as a treatment regime for COVID-19 [65]. However, there exist some considerable remarks that the anti-viral mechanism of action of these drugs against SARS-CoV-2 or their probable theraputic effects to reduce the pathological events of COVID-19 remains unknown. Besides, the use of both drugs has been reported to be associated with some fatal side effects [66,67]. While the transplantation of different types of stem cells has been proposed to improve the outcome of COVID-19 [68], the use of stem cells has generally been known to be associated with the risk of developing tumor growth and metastasis [69]. However, there has been some mounting optimism generated on the implementation of the aforementioned drugs and cell-based therapeutics against COVID-19 with stringent regulation and safety guidelines.

In 2008, the FDA indicated the potential dangers of the BoNT as a therapeutic agent and it further claimed that BoNT could spread beyond the injection site [70,71]. Notably, high doses of BoNT have been known to elicit adverse effects in many organs and tissues including the muscle, lungs and brain [13]. However, toxic effect, if any, found due to the treatment using a mild dose of BoNT could be neutralized using available antibodies against BoNT [72]. Besides, the implementation of antioxidants along with the BoNT treatment has also been reported to minimize its side effects [73]. Moreover, it has been clearly reported that the adverse effects of therapeutic BoNT are temporary and reversible [74]. The use of BoNT at a very low dose has been reported to be comparatively safe [12,13,47,53]. It has been repeatedly demonstrated that very mild doses of BoNT can attenuate many human diseases even at 10 to 20 units [12,13,45,75]. Eventually, a mild dose of BoNT injection has been an accepted practice for the aesthetic procedure in healthy individuals despite some rare reports on its adverse effects depending upon some criteria [11,13,51,53]. A very recent retrospective study by Chiu SY in 2020 indicates that the FDA approved 400 units of BoNT as a maximum dose per treatment session to be implemented for the patients with neurological deficits with a 3-month interval [76]. Even such a high-end dose of BoNT has been reported to improve the functional outcome in patients without any obvious adverse effects [76]. Therefore, a mild dose of BoNT can be translated for the benefit of individuals with COVID-19. Considering the spreading nature of BoNT from the injection site to distal areas [71], a mild dose of BoNT can be expected to yield omnipresent positive effects in many organs that are known to be affected by COVID-19. Taken together, a mild dose of BoNT can be repurposed to combat the pathological stigma associated with multiple organ defects resulting from COVID-19. However, side effects that could arise from the use of BoNT may not be completely ignored. Given that, stringent implementation of safety measures and the therapeutic regime of BoNT against the refractory disease like COVID-19 need to be envisioned. For the optimization of therapeutic dose and clinical procedure

for the BoNT-based therapy, administration paradigms, diagnostics measures and expected outcomes in different subjects with COVID-19 need to be outlined and designated in accordance with established experimental data, preclinical studies and human clinical trials under the regulation and guidelines of the global drug authorities, scientific bodies and health care associations. The human body and physiology have the tremendous ability for spontaneous recovery against many viral infections by a given time frame. Hence, a significant proportion of individuals affected by SARS-CoV-2 have recovered from the dreadful COVID-19 that would shed insight into the underlying mechanism of the immunogenicity and signify the possibilities for drug discovery. However, there is an urgent and unmet therapeutic need for the individuals with COVID-19 who are at a critical stage and to diminish the mortality rate, for which identification and perspectives on the candidate drugs and approaches including the therapeutic BoNT have become highly important. Future experiments directed towards COVID-19 are needed however to validate the proposed therapeutic effect of drugs like BoNT (Figs. 1 and 2).

5. Conclusion

The present exponential incessant in COVID-19 requires ultimate eradication therapy. While plans like nation-wide lockdown, social distancing and self-quarantine have been imposed by many countries to manage the spread of SARS-CoV-2, the establishment of vaccines, identifying the pharmacological strategies and disease modifying therapies to halt the course of COVID-19 has been accelerated. Among them, implementations of ACE2 inhibitors [50], hydroxychloroquine with azithromycin [65], enriched plasma from COVID-19 survivors [77], mesenchymal stem cell therapy [68] and antiviral drugs of HIV treatment like Ivermectin [78] have gained the front-line attention but their therapeutic efficacy needs to be tested against COVID-19. Adding to that, therapeutic BoNT, regarded as a magic bullet appears to have a proven curative effect against many explicated symptoms of COVID-19 including the respiratory failure, cardiac defects and neurological deficits. Importantly, therapeutic BoNT has the capacity to migrate from intramuscular injection site to the brain and other organs [71]. Therapeutic BoNT is relatively safe and the beneficial effect of a single therapeutic dose of BoNT appears to be long lasting [79]. The therapeutic forms of BoNT are available under the brand names like BOTOX® or OnabotulinumtoxinA, Dysport, Bocouture and Jeuveau in all countries. Thus, this article strongly proposes the notion that therapeutic forms of BoNT can also be considered as a potent treatment against COVID-19, however with high precautionary measures.

Declaration of Competing Interest

The author declares no competing interest.

Acknowledgments

MK has been supported by the Faculty Recharge Programme, University Grants Commission (UGC-FRP), New Delhi, India. The author acknowledges a research grant (SERB-EEQ/2016/000639) and an Early Career Research Award (SERB-ECR/2016/000741) from Science and Engineering Research Board (SERB) under the Department of Science and Technology (DST), Government of India, UGC-SAP, DST-FIST for the infrastructure of the Department of Animal Science, Bharathidasan University.

Author would like to thank Miss Risna Kanjirassery Radhakrishnan for reading the manuscript and providing helpful suggestions for the revision.

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