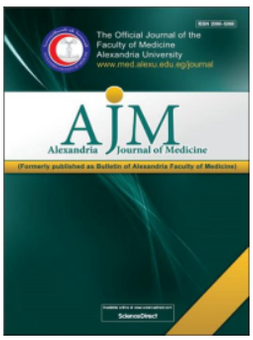

Alexandria Journal of Medicine

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/tajm20

Imatinib a Tyrosine Kinase Inhibitor: a potential treatment for SARS- COV-2 induced pneumonia

Hany Samir ASSAAD & Samir ASSAAD-KHALIL

To cite this article: Hany Samir ASSAAD & Samir ASSAAD-KHALIL (2020) Imatinib a Tyrosine Kinase Inhibitor: a potential treatment for SARS- COV-2 induced pneumonia, Alexandria Journal of Medicine, 56:1, 68-72, DOI: 10.1080/20905068.2020.1778417

To link to this article: https://doi.org/10.1080/20905068.2020.1778417

ALEXANDRIA JOURNAL OF MEDICINE
2020, VOL. 56, NO. 1, 68–72
https://doi.org/10.1080/20905068.2020.1778417

Taylor & Francis
Taylor & Francis Group

MINIREVIEW

Imatinib a Tyrosine Kinase Inhibitor: a potential treatment for SARS- COV-2 induced pneumonia

Hany Samir ASSAAD[a] and Samir ASSAAD-KHALIL[b]

[a]Department of Critical Care Medicine, Faculty of Medicine, Alexandria University, Alexandria, Egypt; [b]Department of Internal Medicine, Faculty of Medicine, Alexandria University, Alexandria, Egypt

ABSTRACT

Introduction: As the coronavirus disease (COVID-19) spreads worldwide, awaiting the development of a vaccine, researchers are looking among the arsenal of available drugs, for a potential cure or medication to improve patients' outcome. A highly elevated levels of cytokines in COVID-19 patients requiring ICU admission, has suggested that a "cytokine storm" was associated with disease severity.

Methods: We summarize published key findings about imatinib, aiming to rationalize its use as a potential pharmacologic treatment for COVID-19.

Results: Data from cellular, animal models and clinical trials, showed a beneficial role of tyrosine kinase inhibitors in the regulation of inflammation, the maintenance of endothelial barrier integrity, as well as the expression of antiviral properties. This data is especially derived from imatinib, the most studied Abl family kinase inhibitor, that is currently in clinical use for multiple medical conditions.

Discussion: Based on this encouraging data, we hypothesize that imatinib might be beneficial for the treatment of patients with SARS-CoV-2 pneumonia, in the aim of preventing disease progression into the severe phenotype of hypoxic respiratory failure and acute respiratory distress syndrome. This concept can be considered for evaluation in a randomized controlled study.

ARTICLE HISTORY
Received 7 April 2020
Accepted 1 June 2020

KEYWORDS
SARS-CoV-2; COVID-19; Acute respiratory distress syndrome; Tyrosine Kinase Inhibitor; Imatinib

1. Introduction

The recently identified coronavirus disease 2019 (COVID-19), which first appeared in Wuhan, China, in December 2019, has rapidly increased in epidemic scale to become a worldwide major health threat[1]. The virus has shown a high transmission rate with a heterogeneous spectrum of clinical presentations; from mild flu-like symptoms to severe pneumonia, hypoxemic respiratory failure and acute respiratory distress syndrome (ARDS)[1].

ARDS is a life-threatening lung condition, associated with profound hypoxia requiring mechanical ventilation and accounting for mortality of most viral respiratory infections[2].

Medication aiming to prevent disease progression into severe phenotypes might have a major impact on patients' outcome and on the optimizing of medical resources utilization.

1.1. The pathogenesis of COVID-19

Angiotensin-converting enzyme 2 (ACE2), which has a protective role against acute lung injury (ALI)[3], is the main cellular receptor for SARS-CoV2[4]. When bonded by the virus spike protein, ACE2 is down-regulated, leading to an increase in angiotensin II and an increased pulmonary vascular permeability, pulmonary edema, and reduced lung function [5,6].

1.2. SARS-CoV-2 mediated inflammatory response

The SARS-CoV-2 mediated inflammatory response can be explained by various mechanisms. The initial rapid viral replication causes massive epithelial and endothelial cell death, subsequently causing vascular leakage. Also, the viral infection induces pyroptosis of macrophages and lymphocytes, which can be triggering the production of exuberant pro – inflammatory cytokines and chemokines[7].

An antibody-dependent enhancement mechanism has also been proposed, promoting cellular uptake of infectious virus–antibody complexes, facilitating a persistent viral replication in the lungs, leading to an extensive inflammatory response[7].

1.3. Role of cytokines in disease progression

Cytokines are a group of structurally unrelated proteins that are categorized based on their binding to distinct receptors, including the tyrosine kinase superfamily, which are important mediators of the signaling

CONTACT Hany Samir ASSAAD assaadhany@gmail.com Faculty of Medicine, Champollion Street, El-Khartoum Square, El Azareeta Medical Campus, Alexandria, Egypt

cascade and key role determinants of diverse biological processes[8].

Patients infected with SARS-COV-2 who showed severe symptoms requiring ICU admission had higher levels of cytokines than did those not requiring ICU admission. This is suggesting that a "cytokine storm" was associated with the severity of the disease and its progression into ARDS[9].

1.4. Current proposed treatments for COVID-19

Currently, there are no specific antiviral drugs or vaccines for the control of COVID-19. Symptomatic & supportive treatment strategies are recommended in clinical practice.

Meanwhile, based on previous experience during the outbreak of SARS-CoV & MERS-CoV, medication with potential benefit have been proposed, aiming to either abolish viral replication or to prevent disease progression.

Treatment with hydroxychloroquine[10], and the combination of lopinavir/ritonavir have been proposed for their antiviral properties[11]. Limited data derived from pilot studies are available about the efficacy of these proposed molecules in the treatment of SARS-COV-2 infection.

The use of systemic anti-inflammatory drugs to reduce cytokine storm is also a potential therapeutic strategy. Corticosteroids were used frequently for possible benefit on reducing inflammation-induced lung injury. However, current evidence has shown no effect on mortality but rather delay in viral clearance, calling for further studies to assess the validity of their systematic use[12].

Interleukin-6 inhibitors, interferon beta, and bevacizumab are proposed biological treatments, aiming to prevent severe damage to lung tissue caused by the cytokine release[13].

1.5. Potential role of protein tyrosine kinases in pulmonary disease

Protein tyrosine kinases (PTK) play a critical role in cellular homeostasis and adaptation to the external environment through diverse cellular processes, such as proliferation, differentiation, migration, inflammation, and maintenance of cellular barrier integrity [14,15]. Given these key regulatory functions, PTKs dysregulation might play an important role in the pathogenesis of many pulmonary diseases, with overlap in various disease states, suggesting their wide-range role as potential therapeutic targets[16].

1.5.1. Background on imatinib

In the early 2000s, successful tyrosine kinase inhibition by imatinib leads to its FDA approval for the treatment of chronic myelogenous leukemia (CML) and provided strong evidence that targeting kinases was not only feasible but could be game-changing[17].

Although imatinib was originally designed to inhibit the BCR-Abl fusion protein, it also inhibits several other kinases including c-Abl, Abl-related gene (Arg), c-kit, and platelet-derived growth factor receptor (PDGFR), involved in regulating vascular permeability[18]. These properties are suggesting that imatinib may have pleiotropic effects on vascular function; a potential role in attenuating inflammation and restoring vascular integrity in inflammatory vascular leak syndromes[18].

1.6. Preclinical studies on imatinib in pulmonary disease

In a clinically relevant animal model of ALI, imatinib attenuated LPS and ventilator-induced lung injury (VILI). Imatinib significantly decreased bronchoalveolar lavage (BAL) proteins and total cells, with a substantial, more than 50% & 88% decrease in total neutrophils TNF-α, respectively [19]. Additionally, despite being given 4 h after the onset of injury, imatinib retained its protective effects and attenuated vascular leak as measured by the significant reduction of BAL total protein & albumin content[19].

The results of this study suggest that imatinib attenuates the inflammation and the vascular leak induced by LPS when combined with VILI and that these protective effects outweigh its potentially deleterious effect in VILI alone, previously reported by the same working group[20].

Evidence from multiple groups has confirmed the ability of imatinib to attenuate vascular permeability induced by diverse stimuli including thrombin, histamine, VEGF, LPS, and reactive oxygen species (ROS) [21,22].

1.7. Clinical experience with imatinib in pulmonary disease

A series of case reports has supported the potential role of targeting Abl kinases to regulate vascular permeability, in which imatinib therapy was associated with rapid resolution of pulmonary and systemic vascular leak. [23–25]

In a randomized controlled trial (RCT) on 62 patients with severe asthma, the use of imatinib inhibited mast cells over activation and was correlated with physiological improvements[26].

In a multicentric RCT conducted in 71 centers (14 countries) with 201 patients with pulmonary artery hypertension, imatinib showed a significant improvement in pulmonary artery pressure parameters, higher reduction in ProBNP levels, as well as clinical improvement evaluated by 6 MW test[27].

In contrast, long-term imatinib treatment in patients with idiopathic pulmonary fibrosis (IPF) did not significantly improve functional capacity nor patients survival versus placebo[28].

Additionally, contrary to its barrier-protective effects, periorbital, subcutaneous edema, as well as pleural and pericardial effusions have been reported as side effects in patients receiving imatinib in certain clinical contexts[17].

1.8. Anti-viral properties of imatinib

The potential antiviral properties of imatinib have been previously demonstrated in pre-clinical laboratory studies, where it showed a potent inhibitory effect on SARS-CoV & MERS-CoV, replication in vitro, mainly through its Abl2 protein kinase inhibition [29,30].

The antiviral activity of imatinib seems to occur at the early stages of infection, after cellular internalization and endosomal trafficking, by inhibiting fusion of the virus at the endosomal membrane[30].

1.9. Potential imatinib-related pulmonary complications

A potential risk of pulmonary complications arising from the use of TKIs has been previously reported. Despite the benefits of TKIs in diseases such as pulmonary hypertension and pulmonary fibrosis, few case reports have paradoxically highlighted their capability to induce interstitial lung disease (ILD). [31]

Imatinib is generally well tolerated, and grade 3 and 4 non-hematologic toxicities are uncommon[32]. In a retrospective analysis of approximately 5500 patients given imatinib for hematological disorders in Japan, 27 patients were diagnosed to have developed drug – induced ILD [33,34]. The median period until development of ILD was 49 days (range: 10–282 days) and the median daily dose of imatinib was 400 mg (range: 200–600 mg) at the time ILD was diagnosed. None has developed diffuse alveolar damage pattern. Most of these patients responded well to corticosteroid treatment, dose reduction, or discontinuation of the imatinib treatment. [33]

1.10. Other Protein Kinases inhibitors with anti-inflammatory effect

Since the development of targeted TKIs, they largely changed the treatment options for diverse disease conditions, ranging from cancer to inflammatory and autoimmune diseases [33,35]. The first developed targeted TKI was imatinib in 2001, yet other TKIs have been also clinically studied for their anti-inflammatory effect and potential use in pulmonary diseases, including nintedanib, dasatinib, nilotinib, sorafenib, and saracatinib[16]. Among these, nintedanib has received the FDA approval in 2014, for the treatment of IPF[36].

Potent Janus Kinase inhibitors; baricitinib & ruxolitinib, have been suggested as possible treatment for SARS-COV-2 infection[13]. However, concerns were raised about their inhibition of a variety of inflammatory cytokines including INF-a, which plays an important role in curbing virus activity[13].

2. Conclusion

Data from cellular, animal models, and clinical trials showed a beneficial role of TKI in the regulation of inflammation, the maintenance of endothelial barrier integrity, as well as the expression of antiviral properties. This encouraging data is especially derived from imatinib, the most studied Abl family kinase inhibitor, that is currently in clinical use for multiple medical conditions. We hypothesize that imatinib might be beneficial for the treatment of SARS-CoV-2 infection and can be considered for evaluation in a randomized controlled study in COVID-19 patients with moderate and severe pneumonia, for the prevention of disease progression into ARDS.

Acknowledgments

None

Disclosure statement

The authors declare no conflicts of interest or relationship with industry.

Notes on contributors

Dr. Hany Samir ASSAAD, lecturer at the Faculty of Medicine Alexandria University, director of the heart failure CARE Program at Alhyatt Heart & Vascular Center, Alexandria, Egypt. After receiving his medical degree from the Faculty of Medicine, Alexandria University, Egypt, he completed his residency and obtained his M.Sc. in collaboration with the University of Chicago, USA & then he pursued with his PhD in Critical Care Medicine, serving as a lecturer at the department. He completed his fellowship training in prestigious centers in France: Rangueil University Hospital, Pitie Salpetriere & Dubos Paris Hospitals, got certified from the Toulouse III Paul Sabatier University, France, and later at Paris Descartes. University, France, when he also fulfilled his PhD degree as a joint collaboration.

Samir ASSAAD-KHALIL is a Emeritus Professor at the Faculty of Medicine, Alexandria University in Egypt. He studied at the University of Alexandria between 1965 and 1982 (Faculty of Medicine MB. Ch. B, DM and MD/PhD Internal Medicine); Rostock University Germany (PhD Thesis) and Post-doctoral mission in Paris University, France in 1983. Within the academia, Prof Assaad-Khalil rose up the ranks from a Demonstrator to Head of the Department of Internal Medicine, and Head of the Unit of Diabetes and Metabolism. Prof. Assaad-Khalil's credentials as a researcher cover an 20 projects conducted in Egypt, Africa, Europe, North & South America and Asia. He has to his credit, multiple awards and grants. He has been instrumental in the establishment of the many national and international societies. He founded the Centre for Foot Care in Alexandria, Egypt and helped in founding similar centers in China, Zimbabwe and Ecuador with the help of the

BRIDGES/ IDF. He also shared in the foundation of Alexandria University CRC and two NGO hospitals in Alexandria. He is the Editor-in-Chief of the Journal of the Egyptian Association of Endocrinology, Diabetes & Metabolism. He has penned many scientific publications and authored/co-authored books on diabetes, lipids and immunology.

ORCID

Hany Samir ASSAAD http://orcid.org/0000-0002-1501-9033

References

[1] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497–506.
[2] Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome. N Engl J Med. 2017;377:562–572.
[3] Imai Y, Kuba K, Rao S, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature. 2005;436(7047):112–116.
[4] Hoffmann M, Kleine-Weber H, Schoroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271–280.e8.
[5] Clerkin KJ, Fried JA, Raikhelkar J, et al. Coronavirus disease 2019 (COVID-19) and cardiovascular disease. Circulation. 2020 Mar 21.; published online. DOI:10.1161/CIRCULATIONAHA.120.046941.
[6] Cheng H, Wang Y, Wang GQ. Organ-protective effect of angiotensin-converting enzyme 2 and its effect on the prognosis of COVID-19. J Med Virol. 2020 Mar 27; DOI:10.1002/jmv.25785. Epub ahead of print. PMID: 32221983.
[7] Fu Y, Cheng Y, Wu Y. Understanding SARS-CoV-2-mediated inflammatory responses: from mechanisms to potential therapeutic tools. Virol Sin. 2020 Mar 3.; published online. DOI:10.1007/s12250-020-00207-4
[8] Morán G, Parra-Medina R, Cardona A, et al. Cytokines, chemokines and growth factors. El Rosario University Press; 2013. [cited 2020 Apr 1]. https://www.ncbi.nlm.nih.gov/books/NBK459450/
[9] Zhang W, Zhao Y, Zhang F, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the experience of clinical immunologists from China. Clin Immunol. 2020 Mar 25.;214:108393. published online.
[10] Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID- 19: results of a randomized clinical trial. MedRxiv. 2020 April 10. doi:10.1101/2020.03.22.20040758.
[11] Cao B, Wang Y, Wen D, et al. A trial of Lopinavir–Ritonavir in adults hospitalized with severe Covid-19. N Engl J Med. 2020 Mar 18.;382(19):1787–1799. published online.
[12] Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet. 2020;395:473–475.
[13] Stebbing J, Phelan A, Griffin I, et al. COVID-19: combining antiviral and anti- inflammatory treatments. Lancet Infect Dis. 2020;20(4):400–402.
[14] Hunter T. Signaling–2000 and beyond. Cell. 2000;100:113–127.
[15] Cohen P. Protein kinases — the major drug targets of the twenty-first century? Nat Rev Drug Discov. 2002;1(4):309–315.
[16] Aschner Y, Downey GP. The Importance of Tyrosine Phosphorylation control of cellular signaling pathways in respiratory disease: pY and pY Not. Am J Respir Cell Mol Biol. 2018;59(5):535–547.
[17] Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med. 2001;344(14):1031–1037.
[18] Rix U, Hantschel O, Dürnberger G, et al. Chemical proteomic profiles of the BCR-ABL inhibitors imatinib, nilotinib, and dasatinib reveal novel kinase and non kinase targets. Blood. 2007;110(12):4055–4063.
[19] Rizzo AN, Sammani S, Esquinca AE, et al. Imatinib attenuates inflammation and vascular leak in a clinically relevant two-hit model of acute lung injury. Am J Physiol Lung Cell Mol Physiol. 2015;309(11):L1294–L1304.
[20] Letsiou E, Rizzo A, Sammani S, et al. Differential and opposing effects of imatinib on LPS- and ventilator-induced lung injury. Am J Physiol Lung Cell Mol Physiol. 2014;308(3):L259–L269.
[21] Aman J, van Bezu J, Damanafshan A, et al. Effective treatment of edema and endothelial barrier dysfunction with imatinib. Circulation. 2012;126:2728–2738.
[22] Stephens R, Servinsky L, Rentsendorj O, et al. Protein kinase g increases antioxidant function in lung microvascular endothelial cells by inhibiting the c-abl tyrosine kinase. Am J Physiol Cell Physiol. 2014;306(6):C559–C569.
[23] Overbeek M, Van Nieuw Amerongen G, Boonstra A, et al. Possible role of imatinib in clinical pulmonary veno-occlusive disease. Eur Respir J. 2008;32:232–235.
[24] Carnevale-Schianca F, Gallo S, Rota-Scalabrini D, et al. Complete resolution of life threatening bleomycin-induced pneumonitis after treatment with imatinib mesylate in a patient with Hodgkin's lymphoma: hope for severe chemotherapy-induced toxicity? J Clin Oncol. 2011;29:e691–e693.
[25] Aman J, Peters M, Weenink C, et al. Reversal of vascular leak with imatinib. Am J Respir Crit Care Med. 2013;188:1171–1173.
[26] Cahill KN, Katz HR, Cui J, et al. Effect of KIT Inhibition by Imatinib on airway mast cells in patients with severe refractory asthma (KIA). J Allergy Clin Immunol. 2019;143(2):794–797.e10.
[27] Hoeper MM, Barst RJ, Bourge RC, et al. Imatinib mesylate as add-on therapy for pulmonary arterial hypertension: results of the randomized IMPRES study. Circulation. 2013;127(10):1128–1138.
[28] Daniels CE, Lasky JA, Limper AH, et al. Imatinib treatment for Idiopathic Pulmonary Fibrosis randomized placebo-controlled trial results. Am J Respir Crit Care Med. 2010;181:604–610.
[29] Coleman C, Sisk J, Mingo R, et al. Abelson Kinase inhibitors are potent inhibitors of severe acute respiratory syndrome coronavirus and middle east respiratory syndrome coronavirus fusion. J Virol. 2016;90(19):8924–8933.
[30] Dyall J, Coleman C, Hart B, et al. Repurposing of clinically developed drugs for treatment of middle east respiratory syndrome coronavirus infection. Antimicrob Agents Chemother. 2014;58(8):4885–4893.

[31] Peerzada M, Spiro T, Daw H. Pulmonary toxicities of tyrosine kinase inhibitors. Clin Adv Hematol Oncol. 2001;9(11):824–836.
[32] Kantarjian H, Sawyers C, Hochhaus A, et al. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. N Engl J Med. 2002;346:645–652.
[33] Ohnishi K, Sakai F, Kudoh S, et al. Twenty-seven cases of drug-induced interstitial lung disease associated with imatinib mesylate. Leukemia. 2006;20:1162–1164.
[34] Patterson H, Nibbs R, McInnes I, et al. Protein kinase inhibitors in the treatment of inflammatory and autoimmune diseases. Clin Exp Immunol. 2014;176:1–10. 163.
[35] Thomas A, Rajan A, Giaccone G. Tyrosine kinase inhibitors in lung cancer. Hematol Oncol Clin North Am. 2012;26:589–605.
[36] Richeldi L, Du Bois R, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2071–2082.