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Letter to the Editor

SARS-CoV-2 (COVID-19) and Chronic Myeloid Leukemia (CML): a Case Report and Review of ABL Kinase Involvement in Viral Infection

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To the editor.

In the past two decades, coronaviruses have emerged as deadly agents, responsible for mild upper respiratory tract infections to life-threatening acute severe respiratory distress and appear to threaten also hematologic patients.[1]

Belonging to the Coronaviridae family, coronaviruses are positive, single-stranded RNA viruses surrounded by an envelope containing transmembrane spikes that anchor to infected cells.[2] They were first identified in the 1930s as responsible for animal bronchitis and gastroenteritis.[3] Human coronaviruses were discovered in the 1960s as the cause of the common cold, and other, more aggressive human coronaviruses have been subsequently identified. Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), was reported in 2002 as being responsible for the highly pathogenic infection that emerged in the Chinese Guandong region, rapidly spreading to southeast Asia and Canada, resulting in 8,273 infected and 775 deaths. (9% lethality).[4] Ten years later, a novel coronavirus with a similar respiratory target, was first detected in Jedda, Saudi Arabia, and for this named Middle East Respiratory Syndrome coronavirus (MERS-CoV). Two additional MERS outbreaks were reported in 2015 and 2018, affecting 2,494 cases in 27 countries, with a very high case fatality rate (858 deaths; 37% mortality).[5]

The recently discovered virus SARS-CoV-2 (COVID-19) is a previously unknown strain of the SARS-related coronaviruses. It was first identified in 2019, when an outbreak of pneumonia of unknown origin was reported in Wuhan, Hubei region, China. Bronchoalveolar lavage fluids from infected patients inoculated into alveolar cell lines led to the isolation and identification of the SARS-CoV-2 coronavirus.[6]

The SARS-CoV-2 virus appears to have a high infection rate. Its reproduction number (R_o) has been estimated between 1.4 and 3.9, meaning that each infection produces 1 to 4 new infections when no members of the community are immune, and no preventive measures are taken.[7]

The infection caused by SARS-CoV-2 is primarily characterized by flu-like symptoms with mild to severe respiratory symptoms. Patients developing pneumonia may rapidly worsen and die of multi-organ failure.[8] Advanced age and presence of comorbidities such as diabetes, heart, lung, and kidney disease are correlated with a higher mortality rate and ICU admission.[9] Immunocompromised patients are considered to be at risk of developing severe SARS-CoV-2 symptoms, and international consensus recommendations regarding this population have been issued.[10] The impact of SARS-CoV-2 on the hematologic patient population is, however, not yet known.

We describe here the first report of a Chronic Myeloid Leukemia (CML) patient treated with Dasatinib who presented COVID19 infection.

A pregnant (7 weeks), female patient, aged 26, no comorbidities, was diagnosed with CML, p210, B2A2, in August 2017. Risk scores were low (Sokal 0.5, Euro 204, ELTS 0.6). Because CBC showed 55K WBC, she was placed on interferon-alpha therapy and achieved a complete hematologic response through the delivery of a healthy baby girl at 38 weeks. In March 2018, the patient started dasatinib (100 mg/day). Three months after starting dasatinib, the patient achieved Early Molecular Response, and at +6 months Major Molecular Response. In December 2018 (+9 months), the patient was in deep molecular response (MR4.5) and continuing full-dose dasatinib therapy. The patient regularly followed her CML follow up every three months with proper drug therapy compliance and stable deep response.

On March 7, 2020, the patient's husband presented with high fever (39.5 C) and progressive breathing difficulties for which he was brought to the hospital. The nasal swab to determine SARS-CoV-2 infection

tested positive, and he was placed on oxygen therapy, antibiotics, and Tocilizumab. Five days later, the patient presented with fever (39.4 C) without respiratory symptoms, testing positive on the swab. The patient was treated with antibiotics (amoxicillin and clavulanic acid) for seven days with paracetamol as needed. After four days, the fever cleared, and after two weeks, two separate consecutive swab tests were negative. During this time, she continued treatment with dasatinib at the same dose.

At present, she feels well and continues CML treatment.

Discussion. Therapy with BCR-ABL tyrosine kinase inhibitors (TKI) in CML patients implies a modest increase in the risk of infection, most likely due to off-target inhibition of kinases involved in immune cell function.[11] Neither chronic phase CML nor BCR-ABL tyrosine kinase inhibitors induce a state of clinically significant immune suppression, and no data are suggesting that chronic phase CML patients may be at higher risk of infection by the novel SARS-CoV-2 compared to the general population.[12] Thus, assuming that chronic phase CML patients on TKI are not at higher risk of developing severe SARS-CoV-2 infection, discontinuation of TKI treatment is not recommended prophylactically or in the presence of unconfirmed compatible symptoms of SARS-CoV-2, as it may lead to loss of response and CML relapse/progression, which could be problematic if regular monitoring of CBC counts and BCR-ABL transcripts was reduced due to lack of lab access during the current pandemic. Similarly, in patients with resistance or intolerance to the current TKI, it is not advisable to delay a change in therapy since the results may be compromised. In case of severe SARS-CoV-2, TKI interruption should be discussed on a case-to-case basis.

In the context of the current pandemic, it is essential to note that TKIs have previously been shown to be effective against other coronaviruses. In 2014 a paper was published in which 290 compounds were screened for antiviral activity against MERS-CoV and SARS-CoV. Twenty-seven compounds were identified to be active against both strains. Among those, three inhibitors of the kinase signaling pathway were present, two (imatinib mesylate and dasatinib) that are active against both MERS-CoV and SARS-CoV, and one (nilotinib) that inhibits SARS-CoV only. The authors suggested that the ABL pathway may be essential for the replication of many different virus families and, therefore, inhibitors of this pathway have the potential to be broad-spectrum antivirals. Mechanistic studies revealed that Abl1 tyrosine kinase regulates budding or release of poxviruses and the Ebola virus. These results demonstrate that c-Abl1 kinase signaling pathways play a critical role in viral egress and suggest that these pathways may also be important in coronavirus replication.[13] Follow up research also identified the mechanisms by which TKIs act during coronavirus infection. This work showed that all enveloped viruses, including coronaviruses, must first fuse with cellular membranes or with endosomes prior to injection of viral RNA into the host cytoplasm for replication and that TKIs inhibit this process.[14]

It appears that imatinib has anti-coronavirus activity in two points of the virus life cycle. In the early phases of infection, it inhibits virion fusion with the endosome and subsequent release into the cytoplasm, thus preventing viral entry and viral replication via Abl-mediated cytoskeletal rearrangement. In a later phase of the infection, Abl2 protein expression, which is inhibited by both imatinib and dasatinib, enables SARS-CoV and MERS-CoV replication. These data suggest that Abl2 is a novel host cell protein required for viral growth.[15]

Together these studies recognize a possible protective role of the TKIs against SARS-CoV-2 infection. Even in our patient, although her husband needed hospitalization with respiratory support, together with an older member of the family, the viral infection showed mild symptoms, resolved with non-specific anti-inflammatory therapy and antibiotics.

On March 31st, a protocol was entered in the EudraCT database to test whether treatment with oral imatinib can reduce disease burden in COVID-19. Its full title is:

COUNTER-COVID - Oral imatinib to prevent pulmonary vascular leak in COVID-19 – a randomized, single-blind, placebo-controlled, clinical trial in patients with severe COVID-19 disease. (https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001236-10/NL)

Conclusions. The incidence and severity of SARS-CoV-2 virus infection may not be worse in CML patients who are being treated with TKIs than in virus victims without an underlying CML diagnosis. Moreover, CML patients who contract SARS-CoV-2 may even be protected by TKI therapy.

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References:

1. Han S.B., Shin J.A., Kim S.k., Lee J.W., Lee D.G., Chung N.G., Cho B., Jeong D.C., Kang J.H. Respiratory viral infections in children and adolescents with hematological malignancies. Mediterr J Hematol Infect Dis 2019, 11(1): e2019006 https://doi.org/10.4084/mjhid.2019.006
2. Wu C, Liu Y, Yang Y, Zhang P, Zhong W, Wang Y, et al. (February 2020). "Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods". Acta Pharmaceutica Sinica B https://doi.org/10.1016/j.apsb.2020.02.008
3. McIntosh K (1974). Arber W, Haas R, Henle W, Hofschneider PH, Jerne NK, Koldovský P, Koprowski H, Maaløe O, Rott R (eds.). "Coronaviruses: A Comparative Review". Current Topics in Microbiology and Immunology / Ergebnisse der Mikrobiologie und Immunitätsforschung. Current Topics in Microbiology and Immunology / Ergebnisse der Mikrobiologie und Immunitätsforschung. Berlin, Heidelberg: Springer: 87. https://doi.org/10.1007/978-3-642-65775-7_3
4. WHO. 2003. Summary of probable SARS cases with onset of illness from1 November 2002 to 31 July 2003. http://www.who.int/csr/sars/country/table2004_04_21/en/index.html.
5. Middle East respiratory syndrome coronavirus (MERS-CoV)". World Health Organization. Retrieved 10 April 2017
6. Ciotti M, Angeletti S, Minieri M, Giovannetti M, Benvenuto D, Pascarella S, Sagnelli C, Bianchi M, Bernardini S, Ciccozzi M: COVID-19 Outbreak: An Overview. Chemotherapy 2020. https://doi.org/10.1159/000507423 PMid:32259829
7. Riou J, Althaus CL.. Pattern of early human-to-human transmission of Wuhan 2019 novel coronavirus (2019-nCoV), December 2019 to January 2020. Euro Surveill. 2020;25(4):pii=2000058. https://doi.org/10.2807/1560-7917.ES.2020.25.4.2000058 PMid:32019669 PMCid:PMC7001239
8. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-1069. https://doi.org/10.1001/jama.2020.1585 PMid:32031570
9. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, Cereda D, Coluccello A, Foti G, Fumagalli R, Iotti G, Latronico L, Lorini L, Merler S, Natalini G, Piatti A, Ranieri MV, Scandroglio AM, Storti E, Cecconi M, Pesenti A for the COVID-19 Lombardy ICU Network. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA. Published online April 06, 2020. https://doi.org/10.1001/jama.2020.5394
10. Al-Shamsi HO, Alhazzani W, Alhuraiji A, Coomes EA, Chemaly RF, Almuhanna M, Wolff R, Nuhad IK, Chua MLK, Hotte SJ, Meyers BM, Elfiki T, Curigliano G, Eng C, Grothey A, Xie C. Practical Approach to the Management of Cancer Patients During the Novel Coronavirus Disease 2019 (COVID-19) Pandemic: An International Collaborative Group. Oncologist. 2020 Apr 3 https://doi.org/10.1634/theoncologist.2020-0213 PMid:32243668
11. Winthrop KL, Mariette X, Silva JT, Benamu E, Calabrese LH, Dumusc A, Smolen JS, Aguado JM, Fernández-Ruiz M. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Soluble immune effector molecules [II]: agents targeting interleukins, immunoglobulins and complement factors). Clin Microbiol Infect. 2018;24 Suppl 2:S21-S40. https://doi.org/10.1016/j.cmi.2018.02.002 PMid:29447987
12. Breccia M, Girmenia C, Latagliata R, Loglisci G, Santopietro M, Federico V, Petrucci L, Serrao A, Salaroli A, Alimena G. Low incidence rate of opportunistic and viral infections during imatinib treatment in chronic myeloid leukemia patients in early and late chronic phase. Mediterr J Hematol Infect Dis. 2011;3(1):e2011021. https://doi.org/10.4084/mjhid.2011.021 PMid:21713076 PMCid:PMC3113277
13. Julie Dyall, Christopher M. Coleman, Brit J. Hart, Thiagarajan Venkataraman, Michael R. Holbrook, Jason Kindrachuk, Reed F. Johnson, Gene G. Olinger, Jr., Peter B. Jahrling, Monique Laidlaw, Lisa M. Johansen,Calli M. Lear-Rooney,Pamela J. Glass, Lisa E. Hensley, Matthew B. Frieman. Repurposing of Clinically Developed Drugs for Treatment of MiddleEast Respiratory Syndrome Coronavirus Infection. Antimicrob Agents Chemother. 2014 Aug; 58(8): 4885-4893. https://doi.org/10.1128/AAC.03036-14 PMid:24841273 PMCid:PMC4136000
14. Sisk JM, Frieman MB, Machamer CE. Coronavirus S protein-induced fusion is blocked prior to hemifusion by Abl kinase inhibitors. J Gen Virol. 2018;99(5):619-630. https://doi.org/10.1099/jgv.0.001047 PMid:29557770 PMCid:PMC6537626
15. Coleman CM, Sisk JM, Mingo RM, Nelson EA, White JM, Frieman MB. Abelson kinase inhibitors are potent inhibitors of severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus fusion. J Virol. 2016 Sep 12;90(19):8924-33. https://doi.org/10.1128/JVI.01429-16 PMid:27466418 PMCid:PMC5021412