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Use of JAK STAT Pathway Blocker To Treat COVID19 Patients- The Future of COVID19 Treatment

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ABSTRACT: Corona Virus Disease 2019 (COVID19) is caused by SARS-COV2 which is a RNA type virus and spreads through droplets. COVID 19 is now a pandemic disease. In several researches it has been shown that this virus works through Angiotensin converting enzyme II (ACEII) and its receptor named ACEII receptor and ACE receptor 1 (AT1R). We are considering a new treatment pathway which is blocker of JAK-STAT pathway and STAT2 and STAT 6 pathway. ACE II receptors are expressed via JAK STAT pathway and STAT2, STAT3, STAT6 pathways. So with anti viral therapy, if we provide JAK-STAT pathway inhibitor like Baricitinib and Ruxolitinib then the treatment can show a better prognosis.

Key Words: COVID 19, SARS-COV2 virus, JAK STAT Pathway, Baricitinib and Ruxolitinib.

INTRODUCTION: Since 2003, Corona virus is causing many serious diseases which is a great problem towards public health. The important diseases are Severe Acute Respiratory Syndrome (SARS), Middle east respiratory syndrome (MERS), Corona Virus Disease 19 (COVID19) (1). COVID 19 outbreak has happened in Wuhan, China in December, 2019 and after that this virus has a significant impact in people's health and life. (1). Corona Virus is a Spherical or pleomorphic enveloped particles coantaining positive sense SS RNA associated with a nucleoprotein within a capsid protein compromised of matrix protein. The envelop bears club shaped glycoprotein projection. (2) COVID 19 is caused through SARS-COV2 virus. This virus spreads through droplets and affects mostly our respiratory system. In the research it has been seen that COVID19 works through ACEII enzyme and ACEII enzyme receptors. (3). COVID 19 has a incubation period of 2-14 days and many patients are asymptomatic and around 5%patient goes to severe disease. COVID19 infection has a severe effects on respiratory system, Gastrointestinal system and neurological

impairment. (4). ACE II function and the function of ACEII receptors like AT1R are induced by JAK-STAT pathway. So in the treatment of COVID19 we can use JAK-STAT pathway inhibitor like baricitinib and Ruxolitinib with anti viral drugs.(5) These drugs are mostly anti inflammatory drug and mostly used in to treat Rheumatoid Arthritis. Our this hypothesis is based on this JAK-STAT inhibition pathway which in future can be used in the treatment of COVID19 patients.

JAK-STAT Pathway: Janus Kinase- signal transducer and activator of transcription (JAK-STAT) is a signaling pathway mediated by cytokines derived mediated signals. JAK-STAT pathway works on developmental process, growth regulations and maintenance of homeostasis. There four JAK(Jak1-3, Tyk2) and seven STAT (STAT 1-4, 5A,5B,6). (6)

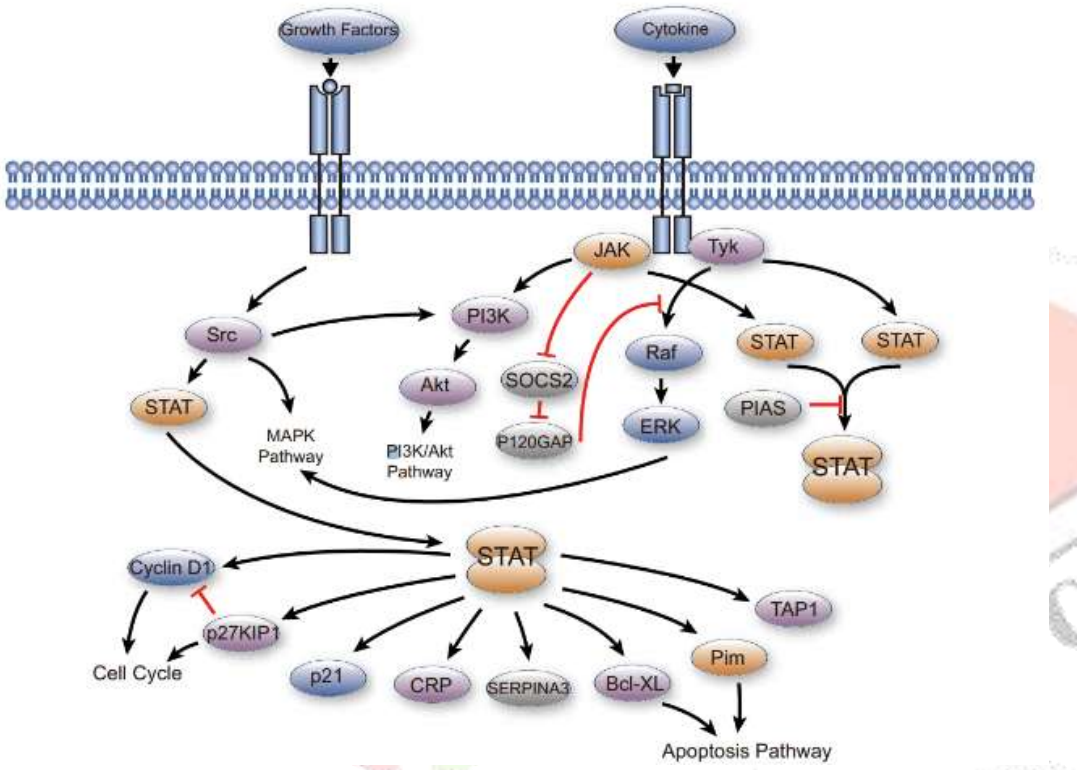

Fig 1 JAK STAT Pathway (6)

Relation to JAK-STAT pathway to COVID19: In a paper of Arindam Banerjee et al it is mentioned that JAK-STAT pathway inhibitor baricitinib may be a very attractive target for the treatment of corona virus infection.(7) Corona Virus cause end organ damage through cytokines storm and JAK-STAT pathway induce that process. (8) Baricitinib and Ruxolitinib both are DMARD drug and have the potential to treat cytokines storms. And Jak Stat pathway also amplify the ACEII and ACEII receptors. COVID19 virus works through this receptors. So JAK STAT pathway blocker are potent drug to treat COVID 19.

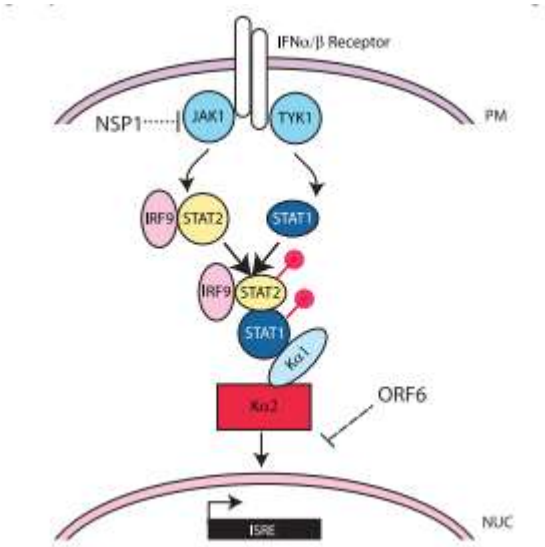

Fig 2. The JAK/STAT signaling pathway and SARS-CoV. The JAK/STAT pathway responds to type I IFN secreted from neighboring cells. The IFN-a/b/ receptor binds to either IFN-a/b or - and signals to the Jak1 or TYK1 kinase. These kinases phosphorylate both STAT1 and STAT2. This phosphorylation induces the complex formation of STAT1/STAT2/IRF9 (the ISGF3 complex) and targets the complex to the nucleus with the help of the import factors KPNA1 (Ka1) and KPNB1 (Kb 1). Once in the nucleus, the complex turns on genes containing an ISRE in their promoter. SARS-CoV proteins have been shown to affect this pathway. NSP1 reduces the levels of Jak1 in the cytoplasm and affects it kinase activity. ORF6 blocks the nuclear import of ISGF3 by reducing the free K 1 in the cytoplasm and retaining it on the ER/Golgi membrane. (9)

Use of JAK-STAT Pathway inhibitor in COVID19 treatment: COVID 19 infection is caused by SARS-COV2 virus. SARS-COV2 virus enters through respiratory tract as a droplets and affects the ACEII enzyme and works through ACEII receptors. STAT 3 is mediated many infections in the human body(10). Studies have shown that JAK-STAT pathway triggered ACEII mediated gene transcription, So JAK-STAT pathway is an amplifier in this pathway. (11). As Baricitinib and Ruxolitinib are two JAK-STAT pathaway inhibitor so they can be used in COVID 19 treatment with antiviral therapy to show good prognosis.

Discussion: According to WHO, Corona Virus is discovered in 1960, and from 2003 SARS, MARS, COVID 19 corona virus related diseases are a big problem for the public health. (1). When SARS-Cov 2 infection occurs then human immune system plays a big role. Some drugs are there which will increase the human immune system and IL10 has a good anti-inflammatory and anti-angiogenic effects (12). In the severe case of COVID 19 severe cytokines storm occurs and respiratory distress and multiple organ disfunction occurs.(13).

ACE2 is a transmembrane protein, through this and its receptor SARS-COV2 shows pathogenesis.(13) The protein is expressed in many lung cells along with type II alveolar cells. Baricitinib is a JAK-STAT pathway inhibitor and mostly used as DMARD or anti Rheumatic drug. It is possible this drug can inhibit cytokine storm as well as reduce the entry of virus and reduce the infectivity towards host cell. (13).

In COVID 19 infection Cytokines like INF gama, IL6 and other storm is seen.(14). As Baricitinib can reduce the cytokines storm so it is a potential drug to treat COVID 19 patients.

Along with its blocking the JAK-STAT pathway i.e the amplification of ACEII and its receptor will reduce. So that the SARS-COV2 virus will be unable to work through this receptors. The severity of the disease will be reduced. In this point of view also it is a potential drug to treat COVID19 patient.

Ruxolitinib is also same potent like Baricitinib theoretically.

Conclusion: Baricitinib and Ruxolitinib are potential JAK-STAT pathway inhibitor and it can be used to treat COVID19 infection with Antiviral drugs.

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Conflict Of Interest: No

Reference:

1. Wang HJ, Du SH, Yue X, Chen CX. Review and Prospect of Pathological Features of Corona Virus Disease. *Fa Yi Xue Za Zhi*. 2020;36(1):16-20. doi:10.12116/j.issn.1004-5619.2020.01.004
2. David A.J, Tyrell, Steven H Myint Medical Microbiology 4th edition, corona virus, Chapter 60
3. Elina Ciaglia, COVID-19 Infection and Circulating ACE2 Levels: Protective Role in Women and Children, Front. Pediatr., 23 April 2020 | https://doi.org/10.3389/fped.2020.00206
4. Bai Y, Yao L, Wei T, Tian F, Jin DY, Chen L, et al. Presumed asymptomatic carrier transmission of COVID-19. JAMA. 2020 Feb;323(14):1406.
5. Seif F, Aazami H, Khoshmirsafa M, et al. JAK Inhibition as a New Treatment Strategy for Patients with COVID-19 [published online ahead of print, 2020 May 11]. *Int Arch Allergy Immunol*. 2020;1-9. doi:10.1159/000508247
6. Bioconnect, lifescience, https://www.bio-connect.nl/jak-stat-signaling-pathway-inhibitors/cnt/page/2514
7. Arindam Banerjee, Rudra Prosad Goswami, Moumita Chatterjee et al. Network theoretic analysis of JAK/STAT pathway and extrapolation to drugs and viruses including COVID-19, 28 April 2020, PREPRINT (Version 1) available at Research Square [+https://doi.org/10.21203/rs.3.rs-25845/v1+]

8. Zhang, W. *et al*. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The Perspectives of clinical immunologists from China.
9. Frieman, Matthew & Baric, Ralph. (2009). Mechanisms of Severe Acute Respiratory Syndrome Pathogenesis and Innate Immunomodulation. Microbiology and molecular biology reviews : MMBR. 72. 672-85, Table of Contents. 10.1128/MMBR.00015-08.
10. Suresh V Kuchipudi, The complex role of STAT 3 in viral infection, Hindawi Publishing Corporation Journal of Immunology Research Volume 2015, Article ID 272359, 9 pages http://dx.doi.org/10.1155/2015/272359
11. Satou, Ryousuke, and Romer A Gonzalez-Villalobos. "JAK-STAT and the renin-angiotensin system: The role of the JAK-STAT pathway in blood pressure and intrarenal renin-angiotensin system regulation." *JAK-STAT* vol. 1,4 (2012): 250-6. doi:10.4161/jkst.22729
12. Dattatreya Mukherjee, Pallab Chakraborty, **"INTERLEUKINS AND CANCER METASTASIS -A BRIEF RELATION "**, International Journal of Creative Research Thoughts (IJCRT), ISSN:2320-2882, Volume.8, Issue 5, pp.1784-1789, May 2020, Available at :http://www.ijcrt.org/papers/IJCRT2005234.pdf
13. https://www.news-medical.net/news/20200512/Could-JAK-blockers-help-treat-COVID-19.aspx
14. Willium Damsky, *"Calming the Cytokine Storm: The Potential Role of JAK Inhibitors in Treating COVID-19" in the May 2020 issue of* The Dermatologis