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CLINICAL AND IMMUNOLOGICAL COMPARISON BETWEEN INFLUENZA VIRUS AND COVID – 19 INFECTION

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SARS-Cov-2 refers to severe acute respiratory syndrome corona virus 2, which is the main reason of corona virus disease 2019 (COVID – 19), WHO recorded more than 347000 death due to the invasion of this virus. One of the most important symptoms appear with this infection is the high level of proinflammatory cytokines especially; IL-6. Beside that huge amounts of macrophage and T helper17 cell could be detected in the lung of the patients suggesting the name of cytokine storm. As other types of viral respiratory infection like Highly pathogenic avian influenza virus, the whole matter is about the competition between the human innate immune response and viral penetration to the lung via the cellular receptors which can recognize the pathogen. Here, there will be a abundant explanation or comparison with some similarities and dissimilarities between influenza A and COVID/19 viral infection which might explain detailed information about the invasion, attack and replication.
In this paper, we tried to review some clinical and immunological similarities and dissimilarities which might appear upon the infection of human with influenza of COVID 19, depending on last findings which had been recorded in different research societies and clinical hospital during last few years hoping to give a clear explanation about the progress of disease and immunological response toward it .

Introduction:
It's well known that the human being suffered from the invasion of both of influenza A virus (IAV) and corona virus (COVID 19) due to the severe defiance between the immune system and the viruses. This defiance will lead to imbalanced situation in immune response to such attack as a kind of response or recruitment against the virus (1,2). The infection with COVID 19 or even with IAV could be accompanied with secondary bacterial infection (3). This review discussed the activation of immune system upon COVID19 infection in parallel with HPAIV infection to see the how can the body develop a appropriate way to resist such infection in order to reach to suitable way to resist this invasion.

Necessary ways of recognizing the progression of disease in COVID 19 with HPAIV together.
In order to reach t the best direction for the treatment of viral infection, it is very important to get a complete idea about the consequences of infection with COVID 19 along with HPAIV, that depends on identifying suitable immunological tests depending on clinical techniques. IFI27 is one of most important substantial candidates which is described as transcriptional factor used in identifying the infection, actually this marker could help in early detection of any viral respiratory disease (4,5). For example, the low levels of lymphocytes count could be found in ICU patients and also for those who were infected with influenza virus off course with the presence of high expression of C reactive protein as an indicator for infection (6,7,8). Like those results or tests used for such detection of flue, we can serve them for detection of COVID 19 using he same markers of different one (9,10).
Scientist found that increased amounts of pro inflammatory cytokines is considered as a fundamental indicator of viral infection as well as a risk marker beside that, IL1β, IL2, IL6, IP10, IL17, TNF-α and MCP1 (11,12,13). other biochemical markers like C reactive protein, and high LDH were depended as important indicators which is combined with viral infection (14, 15).
In a comparison with HPAIV infected persons, the detection of those markers is less sturdy, due to the rare patient that could be infected with HPAIV compared with those of COVID 19 (16). Non the less, results showed that H5N1 patient's high levels of IP10, IL8, CXCL9 and CRP with those who infected with seasonal IAV (17). In Indonesia, more than 22 patients gave high remarkable numbers in D dimer, CRP and Ferritin suggesting a severe support to COVID infection (18,19).

Immune response to the viral infection
It's well known that both COVID 19 and IAV are airborne viruses that can cause severe infection to human via the upper respiratory tract (URT) and lower respiratory tract (LRT) (20,21). It is very important to mention that lung biopsies from human invaded with COVID 19 showed that the LRT are the preferable target of infection and off course IAV (22,23).

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One of the most popular mechanism which might explain the way of infection is that, the alveolar type II pneumocytes (ATII) in the LRT is the best cells required for such infection of both COVID 19 and IAV together (24,25).
Beside ALII, other types were mentioned to accelerate the rate of viral infection like M1 alveolar macrophage (AM) that could give a good push to viral infection by COVID 19 thereby, the activation of AM vial lower endosomal PH leads to activate the membrane binding then viral replication. Other findings proposed that, AM triggering plays important role in directing the viral particle to lysosomal degradation (26). It had been reported that COVID 19 virus has the ability to invade other organs like, small intestine, kidney also, pancreas due to the ability of its binding receptors to interact with cellular receptors of those organs while IAV did not have such ability to infect other organs except the lung (27,28).
After infection, the symptoms start to appear between 5-11 days while in IAV it appears earlier, here we could see fever, cough, nausea and fatigue soar-throat and diarrhea for both viruses (29,30). Like IAV infection, patients with COVID 19 can show clinical variation in severity of infection depending on the stain, for example delta stain produce severe symptoms compared with those infected with omicron stain (31).

Importance of PRRs in defense mechanisms against COVID-19 and HPAIV

To elucidate the mechanism of defense, it is very important to mention that innate immune plays significant role in resisting the viral infection in both of HPAIV and COVID-19 as a fundamental defense strategy (32,33). Actually, many factors were found to disturb or confuse the early response of innate immune response toward viral infection; patients age and some genetic factors led to weaken the activation of immune response. So, the fast development depends on this dangerous factor.
Cellular proteins induction upon the viral infection is the primary sign of starting the transcriptional steps, this activation will restrict the viral replication, promote cell death and amputate the viral distribution. Activation of interferons IFNs depends on (PRRs) in epithelial and immune cells that identify pathogen associated molecular pattern (PAMPs) (34).
Previous studies identified men of those receptors like; RIG-I like receptors (RLRs), toll like receptors (TLRs), nucleotide binding oligomerization domain like receptors (NLRs). When the virus tries to infect the cell, those receptors will be expressed on the surface in order to activate the down-stream proteins like TIR domain containing adaptor inducing interferon β (TRIF), myeloid differentiation primary response 88 (MYD88) which in turn promote the NFκB and interferon regulatory factors (IRFs)which leads to arrange the expression of IL-6, IL-1B, IL-17, IL-8 and Tumor necrosis factors (TNFs) (35).
Many findings explained the role of macrophage from bronchoalveolar lavage fluid in the activation of the inflammatory factors against viral infection there by inducting of IFNs upon COVID-19 attack (36,37). While in IAV, the AMs can recognize the cytoplasmic viral RNA and M2 protein, the release of IFNs, CXCL5,9,10,11, TNF- α and IL factors takes place (38). In acute COVID-19 or HPAIV attack, TLRs participates as a cytoplasmic tracer of viral PAMPs upon the attack but RIG-I stays as the main one for such sensation for both of viruses (39,40). In case of COVID-19 the main mediators which can recognize the infection are; melanoma differentiation associated protein 5 (MDA5) and laboratory of genetic physiology 2 (LGP2) (41).
The mechanism or strategy of defense started with RIG-I interaction with MAVs prior to promotes the TNF, tank binding Kinase1(TBK1), IKK then cellular transcription of Interferon regulatory factors 3, and 7 (IRF3, IRF7) and NFkB (43).
Many findings demonstrated the fundamental importance of IFNs in induction of Janus Kinase (JAK) pathway necessary to upregulation of PRRs and expression of interferon induced genes (ISGs) like; 20-50 oligoadenylate synthetase 1 (OAS1) which provokes viral invasion strategy (43).

Interferons (IFNs) regulatory role

Normally, IFNs is consider as an important reception which activate immunity against viral infection, due to its importance in recruiting signaling cascades against viruses including COVID-19. When they recognize the viral attack there by binding with its receptors on their cellular surface; JAK-STAT kinase will start its work to promotes ISGs which regulate antiviral work strategy. In a fundamental study of COVID-19 infected persons they found that activates IFNs were the main reason behind cellular response. Many signaling cascades like; IFN-α2, IFN-γ carried the signature of IFNs in addition to IFN- α6 and IFNβ. Interestingly; those high levels were correlated with increased expression of CRP which is considered as a primary marker of infection with high levels of neutrophils and lymphocytes (44).
While those patients how suffer from defect especially infants with errors in IFNs response will not be able to resist the viral infection due to in ability to activates the necessary signaling cascade properly (45), the most three familiar errors or deficiencies that restrict cellular immunity against viral infection are; IRF9, IRF7 congenital deficiency and TLR3 were reported when they had been checked in patients suffered from influenza associated pneumonia (46,47,48). Scientists discovered that around 3.5% of acute COVID-19 associated pneumonia patients had accurate IRF7, IRF3, TBL1 and TICAM1 deficiencies (49).

Antibodies of IFNs activated upon viral attack

Auto immune defect recorded large number of autoantibodies (AuAb) that weakened the immune response to COVID-19 infection, among them; type I IFN AuAb in COVID-19 autoimmune B cell phenotypes could induce AuAb against important IFNs like, IFNβ, α, γ or against other cytokines like IL6 (activating upon staphylococcus disease) or

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IL17(activating during mucocutaneous candidiasis) (50). Basically, Zheng M. is considered as the first one who mentioned Type I IFN in patients suffered from systemic lupus erythematous, IFN recipients and thymic dis orders (51).
In other finding, out of 10% of patients with acute COVID-19 pneumonia showed positive results when they checked AuAb in IFN- α2 and IFN-ω, 94% of those patients were men and more that 50% of them were 65 years old. Actually, in this finding they found that all those patients had AuAb against IFN-α types (1,2,4,5,6,7,8,10,13,14,16,17,21) while two of them had AuAb against IFN-β and one against IFN-γ (52).
In another investigation, about 22 patients who had AuAb in APS-1; four of them were died with this virus and the other 19 stayed suffering from the acute symptoms of COVID-19 therefore, they were kept under medical surveillance (53). Indeed, AuAb in IFNs were found to prevent the primary expression of them in nasal epithelium resulted in restricted antiviral barrier (54). Moreover; not only in COVOD-19. AuAb of IFNs effected on other viruses like HPAIV also, in opposite reaction after getting live attenuated yellow fever vaccine (55).
Previously, the finding suggested that IFN plays crucial effect on sustaining viral invade such as HPAIV, via its role in improving a specific reaction after getting attenuated yellow fever vaccine (56), those findings will help in understanding the concept of early vaccination of patients to minimize the risk of viral attack. Moreover, those patients will repress the convalescence period in resisting the viral spread so those medications have a highly importance in enhancement of IFN induction with low percentage of damage (57).
Literary, those findings will support the supportive and therapeutic techniques These findings further help in fine-tuning prophylactic and therapeutic strategies, such as plasma depending Monoclonal AB and positions preventing type I interferon activation including plasmapheresis, plasma blast-depleting monoclonal Abs, and targeted inhibition of type I IFN-responsive B-cells (58).

The role of IFN in treatment of COVID- 19 and HPAIV

Many studies showed that IFN treatment has a basic antiviral activity thereby activation ISG mediated antiviral response in cellular parts. Both of monocytes and macrophages induce CD4, CD8, T cells and B cells. Beside induction of dendritic cells and NK cells, in Hepatitis B and C infection; the IFN-α2 is the main subtypes which will be activated upon infection, other discoveries suggested that IFN beta will be activated in multiple sclerosis (59,60).
Actually, IFN could show certain activity via the enhancement of immune supportive agent that interact with antiviral action or by inducing the histopathological inflammation that restrict the invasion (61). At such level, many recorder side effects could be seen upon the induction of IFNs like; fever, chill and headache although it had been found that viral infection within COVID-19 might delay the induction but is stills necessary to restrict the viral spread then decrease the risk of cellular damage. In another word, there is a severe competition between IFN induction and viral resistance inside our bodies (62,63).
At the same time, other findings mentioned that patients with COVID-19 are suffering from severe complications which lead to attenuate their ability to resist the infection, so; it is a proportional phenomenon.
In the case of IFN-λ which is another type of IFN, we could find different results because of the amazing results because, IFN-λ use gave a weak inflammatory response but high antiviral action than other IFNs, that could be a big benefit in medical use (64). Interestingly, Other in vitro trials showed that IFN-λ Activity Against COVID 19 a remarkable progress toward the infection compared with other IFNs (65,66).
In a clinical survey, vaccinated patients with IFN-λ subtypes got certain clinical progress after seven days of getting this type of medication and about 50 % 0f them showed moderate symptoms of disease after getting this type of vaccine (67).

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