

Association between immune Mediated inflammatory Disease and COVID-19: A Review

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Abstract

COVID-19 outbreak has affected the individuals globally and the individuals with co-morbidities such as diabetes, hypertension, aged individuals with habits such as smoking and Patient with Immune Mediated inflammation (IMI) diseases were considered at the population at higher risk COVID-19 infection and severe progression of the infection. This IMI disease consists of inflammatory bowel disease, connective tissue disease, psoriasis, inflammatory arthritis. Various drug therapies are used for such IMI diseases which include glucocorticoids, cytokine inhibitor, and interleukins which is considered to lower the risk of infection spread. Where as in this review we conclude that the use of glucocorticoids seems to worsen the condition by increase the rate of infection spread and requiring hospitalization, while on other hand the used of cytokine inhibitors and individuals taking methtrexate showed a positive result owing to a good recovers and reduction in the morbidity and mortality

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1. Introduction:

Severe acute respiratory syndrome 2(SARS-CoV-2) had caused a wildfire which was started in December of 2019 since then the invasion has affected the individuals globally. In December 2019 this virus have become a third animal originated virus to have Individual to individual transmission which is main culprit for the spread globally(1).

The common presentation post infection include mild fever, core throat, weakness and in severe cases breathlessness, fatigue and difficulty in activities of daily living. The critical presentation of COVID-19 attributed by an heightened immune reaction excessive generation of pro-inflammatory cytokines

such as interleukin-6, tumor necrotic factor. Growth factors such as granulocytes-macrophages triggering factors and chemokinesis such as Interlukin 8 which is known as cytokine storm(2).

The Virus can affect various of systems of the human body, the common area of infection are in nostrils, nasal cavity, pharnx and larynx, and trachaea, lungs, bronchioles and alveoli , are most commonly affected by SARS-CoV-2 as the virus affect the receptors of the host cells for the enzyme angiotensin converting enzyme 2 (ACE-2) is plentiful on the exterior of type 2 alveolar cells for the lungs(3).

immune mediated inflammatory diseases are any group of any disease or condition with lack of proper etiology, these diseases are presented with inflammatory pathway leading to inflammation which is seen due to improper functioning of the immune system, this disease most often causes end organ damage. However in recent year many researches are conducted on inflammation as it is a prime factor for many autoimmune conditions such as ankylosing spondylitis, psoriasis, psoriatic arthritis, behcet's disease, arthritis, inflammatory bowel disease, connective tissue disease, allergies as well as manu cardiovascular, neuromuscular and infectious diseases. The treatment strategies consist of targeted biologic therapies due to the efficacy, early relief and tolerability, other treatment is anticytokine treatment therapy in multiple organ inflammatory conditions confirmind IMI diseases paradigm. In some patients broad spectrum immune modulators are inculcated which are developed from the monoclonal amd molecular biotechnology and targeted medicinal chemistry. The incidence of IMI diseases is around 80 per 105 person per year and it affect 3 to 7% population. Previous studies showed that presence of IMI disease lead to development of another immune mediated inflammatory disease. Due to long term use of medical therapies the patient overtime become resistant to the drug so to avoid this more precise approach for managing this patient is utilized to prevent development of drug resistance(4–7).

Certain pro inflammatory cytokines prompt in SARS-CoV-2 infection are therapeutic target in the individuals affected with IMI diseases(8,9). These inhibitors are used in treatment of psoriasis, inflammatory bowel disease, arthritis and soft tissue disorders. In this text we outline the information and hazards of COVID-19 infection in patient with IMI diseases of joints, gut and skin(10–14).

2. Morbidities Associated with SARS-CoV-2 Infection:

IMI Diseases are at increased risk of infection, therefore the individuals with coronavirus infection are at risk, whereas the proof for the same is very limited. Individuals suffering from IMI are receive immune mediated therapies such as glucocorticoids, cytokines, interlukines HCQs and the individuals present with other complications like cardiovascular, pulmonary and metabolic which affect the course of the infection. Greater the co morbidities greater is the risk of spread of infection and treatment such as glucocorticoids depresses the immunity and impaires the function of the inborn immunity but hampers the immune cells such as T cells(15) (16).

Certain drugs like cytokine blockers have direct influence of the risk of the infection. There is higher risk of fungal infection with the use of interlukin 7 inhibitors, similiary Janus Kinase Inhibitor on herpes zoster. Data suggest that the above mentioned drugs have a specific effect and do not aid the spread of

infection, the effect of the IMI drugs on the respiratory infection is limited. The pandemic provided the researchers with a opportunity to study the relation between the immune mediated diseases and infection(17) (18,19).

3. Hazards of Severe COVID-19 Outcomes:

The presentation of COVID-19 vary from mild symptom such as fever, sore throat, weakness whie in cases of severe infection the breathlessness, fatigue and hospitalization and death in many cases, the severity of the infection is based the incidence of the virus in the locality, immunization, social behavior and preventive strategies, reliability of the diagnostic methods etc. due to such vast factor the measurement is not always accurate and the results are presented with a bias. One cannot judge the severity of infection based on the Hospitalization alone, various secondary factors plays an important role such as environmental condition, overall health status of the community dwelling individuals, availability of the hospital care for the individuals. Mortality is an indicator to determine the severity of any disease ultimately, but certain underlying factors like presence of co morbidities, demographic and socioeconomic status due to which the disease severity is misjudged. (20,21)

4. Inflammatory Arthritis:

Cohort Studies during pandemic have proved that the inflammatory joint conditions like arthritis, spondylosis and other inflammatory conditions have direct association COVID-19 the individuals with both have require hospitalization in ICU and need ventilator support(22) a study in high incidence rate of inflammatory disease was conducted in Italy during the initial phase of the pandemic, which showed no specific IMI influence the risk of development of COVID-19. Two other studies in different country showed no death associated in one study and only 8 hospitalization(n=955) with mild diseases course(23). Increased risk of COVID-19 related death in individuals with inflammatory joint disease is high as compared to the healthy population. During initial phase various researches are carried out which was mostly focused on the adult population this age group is present with co morbidities which lead to misinterpretation and the second major error is ignoring the effect caused due to secondary exposure which are present as the same manner as the primary exposure(24). Another study conducted in US on the American veterans demonstrate that the hazard of death and hospitalization is higher in individuals with COVID-19 along with inflammatory arthritis(25). The mean age of the population in this was 67.8and most patients were 84.5. Increased rates of COVID-19-related hospitalisation is not necessarily related to increased odds of death in patients with immune-mediated inflammatory diseases(26).

5. Psoriasis:

37% of population in developed countries are on cytokine inhibitor for the treatment of psoriasis. Available literature on psoriasis suggest that the there is no significant increase risk of SARS-CoV-2 infection in the psoriatic population(26–28). A study suggests that higher rate of cytokine usage in individuals suffering from psoriasis and noincreased risk of COVID-19 infection out of total sample size i.e 5206, only 4 patient were admitted to hospital who were presented with other co morbidities like older age due to covid induced pneumonia(27). Individuals affected with psoriasis carry higher burden of metabolic, cardiovascular and pulmonary co morbidities as compared to general population, various

studies suggest that there is correlation of increased risk of COVID-19 infection with psoriasis. Very few population require hospitalization and ICU admission but an observation suggest that the rate is same as compared to general population(29–31).

6. Connective Tissue Disease

Individuals with connective tissue diseases like polymyositis, SLE, etc have high morbidity and mortality rate attributed to infectious diseases. Studies show that there is increased risk of connective tissue disease and immune mediated inflammation as compared to general population(32). one meta analysis conclude that highest prevalence of COVID infection is present in individuals with connective tissue diseases as compared to any other immune mediated inflammation and this population also presented with higher percentage of glucocorticoid usage(25) A comparative study was conducted with IMI disease and COVID-19 and healthy population the result of the study showed that the participants with inflammatory arthritis are at higher risk for covid- infection as compared to individuals with connective tissue disease(34) same results were found in two other studies after adjusting the variable like age gender and co morbidities(35,36). the effect of B-cell depleting therapy on covid is limited and evidence on the connective tissue disease is scarce as compared to other immune mediated inflammatory diseases and covid, more studies can be conducted in the association between connective tissue disease and covid infection spread(36).

7. Inflammatory Bowel Disease

Patient with inflammatory bowel disease were considered as the population at higher risk of covid infection as due to dysfunction of the gut barrier and due to excessive immune modulatory treatment(37). during the initial phase of covid 19 there was huge façade that integrity of the intestinal barrier will be associated with severe covid 19 infection and increased ACE2 receptor in the terminal colon of patient with IMI diseases was observed in experimental settings, and increased gut leakage biomarkers were found in patients with severe COVID-19(38,39). Although some clinical features of covid 19 are widely associated with gastrointestinal involvement. However many studies have proved no association of COVID-19 and inflammatory bowel disease(40).

Diseases such as chron's disease, can be at increased risk because of gut barrier dysfunction and intensive immune modulatory treatments. A study show that there is 10 times increase in the risk of COVID-19 related pneumonia while 5 times increase in risk was seen in the individuals with inflammatory bowel disease consuming glucocorticoids(40). The evidence suggest that the risk and outcome of SARS-CoV-2 is patient with inflammatory bowel disease and general population is same if the patient do not use glucocorticoids and have good disease control and those who are consuming glucocorticoids and poor disease control caution is advised(41,42).

8. Immunomodulatory Treatments

Glucocorticoids:

The high death rate and risk of high dosage of glucocorticoids is long known and the correlative risk related to glucocorticoids use is more than other agents used for IMI(18,43). Implication of systematic dexamethasone in patient without IMI disease result in lower death rate in comparison with glucocorticoids, the the ill effects after the use of glucocorticoids was shown in a study where after the use of glucocorticoid there is increased morbidity in patients(44). A study conducted on 600 patient globally in association with global rheumatology alliance(GRA) the main variables were COVID-19 related hospitalization, cardiovascular, renal, respiratory co morbidities with intake of 10mg prednisone daily which was linked with twice the hazard of hospitalization(45).

Conventional Immunomoulatory drugs

Values on the specific effect on conventional immunomodulatory drugs on infection disease course is scarce. Sulfasalazine use showed poor outcome and increased risk of severe spread of COVID-19 infection having inflammatory bowel disesase(46). A cohort study with inclusion of the individuals with inflammatory bowel disease showed thiopurine monotherapy and combination therapy depicted development of severe infection which lead to hospitalization and admission to ICU and death in most cases. Use of conventional immunomodulatory drugs showed increased risk of severe COVID-19. In addition individuals treated with conventional immunimodulatoey drugs reflected no increased risk of infection. The available evidence conveys that the sulfasalazine and potentially some other immunomodulatory drugs.

Cytokine Inhibitors:

The evidence collected during thr pandemic suggest that the cytokine inhibitors are safe, a report suggest that the increased risk of COVID-19 infection and hospotolization in patient with psoriasis treated with Cytokine inhibitor(26).

In inflammatory joint disease the risk of death due to COVID-19 is significant in individuals who were on glucocorticoids, the disease course showed no alteration upon the use of cytokine inhibitor.

A protective effect of cytokine inhibitor inpatient with ssymptomatic COVID-19 was reported among 2050 patient with inflammatory joint disease. A study found out that the use of cytokine inhibitor is safe for patient with rheumatoid arthritis(23,47). However more precise researched on SARS-CoV-2 infection on patient receive Cytokine inhibitor is required as this drug interfere with antiviral response(48,49). In the pre pandemic phase the usage of cytokine inhibitor has increased the hazards of upper respiratory tract infection associated with psoriasis linked with TNF inhibitor.

Response to SARS-CoV-2 Vaccination

Robust cellular and humoral immune response was seen using the mRNA and vector based vaccine in healthy individuals(50,51) A small study concluded the development of antibodies in response to vaccination and very few researches are available for immune mediated inflammatory disease(52). Impaired response to vaccination is seen in mRNA based vaccine in large population. An observational study was done which included individuals lying in the median age ninety four percent subjects have developed anti SARS-CoV-2 antibodies(53). Individuals who were on immunomodulatory drugs responded poorly to the vaccine as compared to the healthy population, Result of other study suggested slowed and lower antibody reaction i.e. 1 in 10 subjects not having sufficient neutralizing antibody response(54). Individuals with immune mediated diseases showed reduced humoral response to the vaccine after the first dose. 15 percent individuals who were on medication for IMI diseases and those who were on conventional medications have not developed anti SARS-CoV-2 antibodies(55).. In a study done on 82 subjects showed no significant response to the immunization who were on conventional medication for the IMI diseases(56). Population with inflammatory bowel disease responded positively to the mRNA based vaccination who were medication such as infliximab and vedolizumab(57,58). One small study with systemic autoinflammatory syndrome managed with interleukin 1 inhibitor responded positively to the vaccination with no flares in the disease course(59). In future various studies should be conducted to assess the role of T cell reaction on COVID-19 infection to treat the individuals who have humoral non responded, and the ideal time for dose is during the B cell population.

9. Conclusion:

The overall literature suggest that the medication used for IMI disease associated with COVID-19 put the patient at increased risk for SARS-CoV-2 infection and may put the patient in severe COVID-19. The severe COVID-19 infection is associated with cardiovascular, pulmonary, metabolic and systemic comorbidities which leads to hospitalization of the individuals and death sometimes. The review suggest that the intake of glucocorticoids in patient with IMI showed increased inflammation and poor prognosis. While the use of cytokine inhibitors does not seem to affect the severity of the infection in contrast with the glucocorticoids consumption.

The researched mentioned above are from the developed countries that is high income countries with varied IMI diseases, and scarce evidence in the low income countries(60). Low earning countries have already suffered from the infection due to strained health care system, large population, lack of medical assistance in the remote areas and presence of the IMI diseases have made it more difficult in low income countries to tackle the infection as due to poor environmental condition aid the spread the infection and large population make it hard to manage the scenario which is much more less tidies in the high income and developed countries. Cytokine inhibitor have seen to not affect the susceptibility to the infection and severity of the COVID-19 infection. On other hand broad spectrum antibodies like B cell depleting drugs

and glucocorticoids are responsible to suppress the immunity and aid the systemic spread of the infection and leading to hospitalization. Cytokine inhibitor act on the IMI disease thru a specific pathway which do not interfere with the existing immune status and in term showing positive health benefits. B cell depleting therapies, methotrexate or TNF blockers showed poor response to vaccination and poor development of defense against the infection.

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