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COVID-19 AND EMERGENCE OF DILEMMA REGARDING THE SAFE STRATEGY OF DIAGNOSIS AND TREATMENT IN AUTOIMMUNE DISEASES: A MOLECULAR ASPECT

Biochemistry

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ABSTRACT

COVID-19 and Autoimmune disease are present in a patient simultaneously can ruin life because of two reasons chiefly. Firstly diagnosed patient receiving immunosuppressant therapy is simply vulnerable to COVID-19 which generally attacks the immune system. Secondly, those huge undiagnosed symptomatic cases can have the risk of the overactive immune system leading to a Cytokine storm. We look into the molecular basis of both COVID-19 and autoimmune diseases with drugs acting upon them to find out the answer to the questions arising out of the diagnosis and treatment of these cases. It is the ACEII type receptors which are the first contact points of COVID -19 ultimately resulting in the huge proliferation of pro-inflammatory cytokines leading to cytokine storm. Autoimmunity also involves the down regulation of regulatory T-cells and up regulation of T effector cells leading huge cytokine release as comparable to cytokine storm. Then Mechanisms of relevant drugs were studied. We concluded after reviewing the different literature that on the molecular basis of these two groups of diseases screening tests should be suggested to all of the symptomatic cases immediately for both autoimmunity and COVID-19 infected patients and use of rationale drug therapy keeping eye on immunosuppression and cytokine over activity.

KEYWORDS

COVID-19, Cytokine storm, Autoimmunity

INTRODUCTION

The name COVID-19 terrorizes everybody now a day. But its inception was so innocuous that nobody bothered to look for a comprehensive strategy to combat the widespread severity of the disease. COVID -19 is an acute illness caused by a new coronavirus called the SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2).A lot of studies done about its evolution, epidemiology, pathogenesis, and possible preventive and curative strategies. Since it is new to our world, a lot of associated comorbidity related to different immune conditions need to be addressed so that people with preexisting diseases can fight it out against this utter nuisance created by COVID-19. This Review article will look into the COVID-19 and autoimmune disorder simultaneously so that a combat strategy can be developed.

BACKGROUND

WHO officially named the disease as coronavirus disease 2019 (COVID- 19) and Coronavirus Study Group (CSG) of the International Committee proposed to name the new coronavirus as SARS-CoV-2, both issued on 11 February 2020. The Chinese scientists isolated a SARS-CoV-2 from a patient on 7 January 2020 and subsequently, genome sequencing of the SARS-CoV-2 was done [1]. Studies estimated the basic reproduction number (R0) of SARS-CoV-2 to be around 2.2 [2], or even more (range from 1.4 to 6.5) [3], and familial clusters of pneumonia [4]. Human-to-human transmission is seen to be the key feature in this outbreak.

Origin and transmission of SARS-CoV-2

Coronaviruses are positive-sense RNA viruses with envelopes. Human coronaviruses (HCoVs) detected in α coronavirus (HCoV-229E and NL63) and β coronavirus (MERS-CoV, SARS-CoV, HCoV-OC43 and HCoV-HKU1) genera [5]. There are two other strains seen as γ and δ as well but they are chiefly associated with avian transmission and infection.

In Wuhan, a city of China a patient presented with Dyspnea, Fever, Sore throat with acute respiratory distress got admitted in the hospital in late December 2019 and after few days of elaborate study of the patients admitted with similar episodes revealed that it was the β coronavirus of the different genome not seen previously. This isolated novel β -CoV shows 88% identity to the sequence of two bat-derived severe acute respiratory syndromes (SARS)-like coronaviruses, bat-SL-CoVZC45, and bat-SL-CoVZXC21, and about 50% identity to the sequence of MERS-CoV [6]. The novel b-CoV was then named "SARS-CoV-2" by the International Virus Classification Commission.

The viral genome consists of four main structural membrane proteins like a spike (S), envelope (E), nucleocapsid (N) and membrane (M) proteins and several other accessory proteins whose functions are not known. The nonstructural proteins are the major constituents of the viral genome which are responsible for replication and transcription part of the machinery [7,8].

S protein is responsible for its fusion to the alveolar cells via the ACE 2 receptor [9]. Once it is fused it can invade via clathrin-dependent or independent endocytosis process or via furin activated fusion process. [10]. After entry to the cells, the viral genome is released into cytoplasm then structural proteins are formed and after fusion with ER and Golgi body, the vesicles loaded with newly formed viruses are formed [11,12]. Ultimately with the hospitable environment, the virus-containing vesicles are released after fusion with the cell membranes [13].

Antigen Presentation in COVID-19

We all know that once an infectious substance once entered inside the body, it should face our antigen-presenting cells or APCs more specific to say that virus is presented to APCs governed by MHC I and II or Major Histo Compatibility Complex [14]. HLA or Human Leucocyte Antigen designs the MHCs hence any polymorphism in them may help or aggravate the situation and here also autoimmunity comes into picture which is mediated by HLA mediated mutation and reactions as seen in many diseases [15]. In this context, it is also seen that mutation in MBL or Mannose Binding Lectin may be also associated with chances of COVID-19 attack and susceptibility [16].

CYTOKINE STORM

ARDS or Acute Respiratory Distress Syndrome is thought to be the final outcome of many fatal cases associated with COVID-19. The reason behind this ARDS is a Cytokine storm. The list of pro-inflammatory cytokine released by the interaction of T effector cell is quite exhaustive starting with IFN-α, IFN-γ, to IL-6, IL-12, IL-18, IL33, TNFα, TGFβ, etc and chemokine's (CCL2 , CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc.). This molecular event ultimately leads to a severe inflammatory response resulting in multi-organ failure. [17,18-20].

Autoimmune diseases and COVID-19

AS already seen virus can stimulate a terrible cytokine storm in the lung, such as IL-2, IL-6, IL-7, GSCF, IP10, MCP1, MIP1A, and TNFα, followed by the edema, dysfunction of the air exchange, acute respiratory distress syndrome, acute cardiac injury and the secondary

infection [21], which may lead to death. Therefore, avoiding the cytokine storm may be the key to the treatment of HCoV-19 infected patients.

Now what about autoimmunity: Researchers proposed that several molecular mechanisms can govern the autoimmune disease pathogenesis. All of these chiefly centered around one thing that it is the loss of regulation on the part of T-cells creating an overactive state of the immune system in the body. The first theory suggested that helper t-cell tolerance was broken either by bypassing or substituting.

The second one suggesting any self-antigen that was completely sequestrated during development can be presented as to foreign as and when the immune system matures. At the molecular level, it is the over activity of Tcell particularly Teffector or Teff cells and down regulation of Tregulator or Treg cells or suppressor T cells and associated viral infection also can take care of above mechanisms like forming immunologically active unit associated with self-antigen or directly suppressing Suppressor T cell functions causing a cytokine overproduction and stimulation of pro-inflammatory cytokine activation leading to disease progression.

So that it is necessary to develop a strategy to diagnose the autoimmune disease at a very early stage with or without this dreaded viral infection so that a combat strategy can be developed.

Now, what are the safe diagnostic approach to diagnose both COVID and autoimmune disease at a go.

Researchers suggest a rapid antibody test for COVID with anti-nuclear antibody detection by ANA HEp 2 method (Indirect Immuno fluorescence test or IIFT) can be done to ascertain the disease existence and progression.

A little bit about the diagnosis of Autoimmune diseases particularly Connective Tissue Disorders or CTD s are screened by ANA HEp 2 method which is based on simple but very effective observation of thoroughly processed slides under the microscope by indirect immunofluorescence technique, it can describe several distinct patterns thus helping the clinician to chalk out a plan for further strategy regarding diagnosis and treatment algorithm.

Screening by ANA HEp 2 followed by confirmation by line IMMUNOASSAY is the heart of much CTD diagnosis done by Rheumatologists.

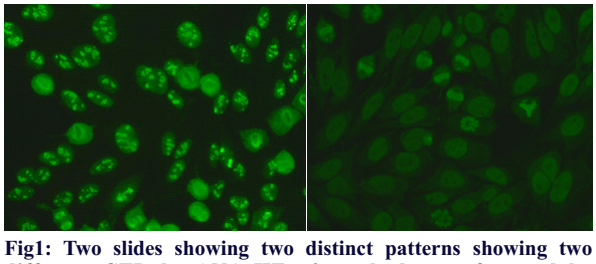

Fig1: Two slides showing two distinct patterns showing two different CTD by ANA HEp 2 method manufactured by EUROIMMUNE, GERMANY, Picture taken from Authors, Laboratory at MCH, Kolkata

Next step of Diagnosis mainly involves Line Immunoassay as depicted in the next figure

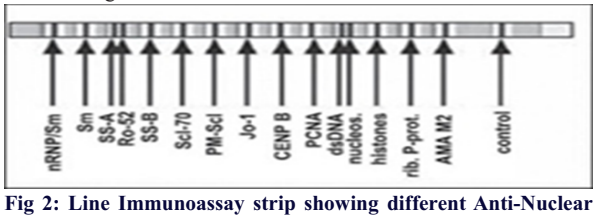

Fig 2: Line Immunoassay strip showing different Anti-Nuclear antibody impregnated in a strip manufactured by EUROIMMUNE, GERMANY,Pic taken from EUROIMMUNE kit literature supplied in Authors' lab.

However, this ocean of autoimmune disease starting from osteoarthritis to Systemic sclerosis and so on encompassing a wide group of population chiefly female, a large number among them are completely dependent on steroids for their simplest of domestic activity.

So with this new lethal COVID-19 is coming up what should be the rationale of treatment of this patient after seeing the activity of COVID-19.

Treatment with steroids can jeopardies the immune system particularly immune response towards invading microorganism and without steroids or other disease-modifying drugs, huge cytokine storm and over activity of immune system can cause havoc if COVID-19 really invading through. So to make a combat strategy we should also look into the molecular mechanism of autoimmunity in detail with respect to understanding the mechanism of drug action.

The drugs can be categorized as Non-Steroidal Anti- Inflammatory Drugs or NSAIDs, Steroidal group of drugs, Certain Disease-Modifying Anti-Rheumatic Drugs or DMARDs and Biologic agents or Novel Drugs.

The Categories of NSAIDs

This group of drugs simply acts as anti-inflammatory agents by virtue of their activity to block pro-inflammatory prostaglandin by inhibition of cyclooxygenase or COX enzyme either by selectively or non-selectively (Rainsford, 2007), thus relieve pain and acts as antipyretic agent. (Simmons et al, 2004) In general, NSAIDs can be again classified into selective and non-selective groups.

Glucocorticoids or Steroidal group

The glucocorticoids were discovered by Hench and Kendal in the 1940s (Hench et al., 1949). Since their inception, their uses were wide starting from anti-rheumatic to drugs against asthma to any kind of severe inflammation owing to their action via AP-1 and nuclear factor nf-κβ to block pro-inflammatory T cell activity and enhance Suppressor CD4+ fox p3 T regulator cell activity. But our concern here is its non-specificity so in a disease like severe COVID-19 how can we simply rely on this group as it can have the potentiality to drag immunological reaction to the lower limit rapidly so that body's reaction against COVID can be severely affected.

Coming to the next group

Conventional Disease-Modifying Anti-Rheumatic Drugs (cDMARDs)

Methotrexate

Methotrexate is considered as the first line of DMARDs because it can inhibit lymphocyte proliferation and helping to curb the formation of pro-inflammatory cytokines as it is the analog and antagonist against folic acid which is considered as raw material for the formation of DNA. The major drawback is its widespread action on growing cells beside other GI symptoms.

Leflunomide

Leflunomide is an isoxazole derivative, acts by blocking the rate-limiting enzyme dihydroorotate dehydrogenase, thus selectively inhibits the synthesis of de novo pyrimidine ribonucleotides such as rUMP (Fox et al., 1999). Because of its selectivity, many clinicians use this drug as first-line therapy in the DMARDs group.

Other DMARDs

Except for methotrexate and leflunomide, other DMARDs, include gold compounds, sulfasalazine, azathioprine, cyclophosphamide, antimalarials, d-penicillamine, cyclosporine, are all the drugs used alternatives to these above two in the treatment of autoimmune inflammatory diseases such as RA (Gabriel et al., 2001).

A special mention is needed for antimalarial drugs for their recent advancement in the treatment of COVID-19. Though no discrete mechanism action elucidated in the field of treatment these drugs showed remarkable activities in many studies.

Antimalarial drugs hydroxychloroquine and chloroquine have the capacity to alter disease progression via their inhibitory action on T cells and B cells (Taherian et al., 2013) and the production of pro-inflammatory cytokines such as TNF, IL-6, and IL-1β (Jang et al., 2006). Both drugs can have some side effects particularly retinopathy and myopathy.

Now we are considering anti-TNF agent and many considered them as

a lifeline for the treatment of Auto immune-mediated CTD in the background of the COVID-19 cloud.

TNF is considered as a master pro-inflammatory cytokine that can stimulate a cascade of reaction to the harbor and nurture other pro-inflammatory cytokines (Moudgil and Choubey, 2011). Consequently, anti-TNF agents have the ability to block the biological function of TNF were used for the therapy of autoimmune inflammatory diseases (Meier et al., 2013).

CONCLUSION DRAWN FROM THIS OVERVIEW

Patients with an autoimmune disorder are vulnerable to COVID-19 because of their undergoing immunosuppressive therapy or in undiagnosed cases where the overactive immune system may cause cytokine storm and increases mortality if COVID-19 invading their defense.

So the strategy should include a test of the symptomatic patients of autoimmunity along with COVID-19 in the form of ANA HEp -2 or line immunoassay act as a screening test for autoimmune connective tissue disease along with rapid antibody and PCR test for COVID-19 if facility permits.

Now the Second strategy should encompass rationale drug therapy which should include a combination of DMARDS and Hydroxychloroquine and try to avoid nonspecific immuno suppressants like systemic steroids to this vulnerable group. A proper algorithm can be developed in near future so that both the drug therapy and diagnosis can be done at mass scale for the patients suffering from auto immune connective tissue disorders and COVID-19 simultaneously.

Last but not the least anti-TNF agents should come into picture more for this group of patients as this group is more target-oriented and selective.

Conflict of Interest: No Such

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