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Covid-19 Infection: The Perspectives on Age-Dependent Difference in Immune Responses and Immunological Strategies to Reduce Viral Burden

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Abstract

Covid-19 is caused by the novel strain of Corona virus named as SARS-CoV-2 because of its homology with SARS infection and it is first detailed in Wuhan, China in December 2019. From that point forward, it has spread globally, already contaminating a large number of individuals worldwide and has been proclaimed as a pandemic by the WHO (World Health Organization) on March 2020. SARS-CoV-2 causes acute respiratory infection with fluctuating seriousness in various age groups, wherein geriatric patents in general will have serious disease. In children it is moderately spread till-date. A few contrasts in the pathogenesis of Covid-19 among pediatric and geriatric patients have been proposed to clarify these differences. Severe Covid-19 disease is associated with high and persistent viral burdens in the elderly patients. Children have strong innate immune response because of trained immunity (secondary to live-vaccines and frequent viral infections), leading to presumably early control of infection at the site of entry and also the risk factors associated with children were very less as compared to elderly individuals. The expression of primary target receptor for SARS-CoV-2, i.e. angiotensin converting enzyme-2 (ACE-2), decreases with age which has lung defensive effects and the severity of the disease can be explained by the presence of enzyme called Furin. Henceforth, this review will highlight the clinical features, disease pathogenesis, age-dependent difference in immune responses and immunological strategies to reduce viral burden.

Keywords: Covid-19; SARS-Cov-2; Immunopathogenesis; Viral burden

Abbreviations

ACE-2: Angiotensin Converting Enzyme-2; ARDS: Acute Respiratory Distress Syndrome; ADE: Antibody Dependent Enhancement; BCG: Bacille Calmette-Guerin; Covid-19: Coronavirus Disease 2019; CDC: Centers for Disease Control and Prevention; CTLs: Cytotoxic T lymphocytes; CCR: CC Chemokine Receptor; CD: Cluster of Differentiation; CXCL: C-X-C Motif Chemokine Ligand; DTH: Delayed Type of Hypersensitivity; G-CSF: Granulocyte Colony Stimulating Factor; HLA: Human Leukocyte Antigen; HCoV: Human Coronavirus; IP-10: Interferon-Gamma Inducible Protein 10 ; IFN: Interferon ; IL: Interleukin ; IgG: Immunoglobulin G ; IgM: Immunoglobulin M ; ICU: Intensive Care Unit ; MERS-CoV: Middle East Respiratory Syndrome Coronavirus ; MHC: Major Histocompatibilty Complex ; MDA5: Melanoma Differentiation-Associated Protein 5 ; MCP1: Monocyte Chemoattractant Protein-1 ; mAbs: Monoclonal Antibodies ; MIP-1A: Macrophage Inflammatory Protein 1 Alpha ; mTOR: Mammalian Target of Rapamycin ; PAMPs: Pathogen-Associated Molecular Patterns ; PRRs: Pathogen Recognition Receptors ; RNA: Ribonucleic Acid ; RBD: Receptor-Binding Domain; rRT-PCR:Real-Time Reverse Transcription Polymerase Chain Reaction; SARS: Severe Acute Respiratory Syndrome; SARS-CoV: Severe Acute Respiratory Syndrome Coronavirus; scFv: Single Chain Variable fragment; TMPRSS2: Transmembrane Protease Serine 2; TNF-alpha: Tumor Necrosis Factor-alpha; TLR: Toll-Like Receptor; TGF-β: Transforming Growth Factor β; T1IFN: Type 1 Interferon; WHO: World Health Organization.

Introduction

The Coronavirus Disease-19 (Covid-19) pandemic brought about by severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), was first announced in Wuhan, China in December 2019. From that point forward, it has spread globally, already contaminating large number of individual worldwide. Starting at 30 June 2020, 213 countries have announced Covid-19 cases, with an all out number that came to above 10.3 million, the most being in the USA (2.6 million), Brazil (1.4 million), Russia (640 thousand), India (548 thousand) and UK (314 thousand). USA has the most elevated number of deaths (126 thousand) followed by Brazil (58 thousand), UK (44 thousand) and Italy (35 thousand). The overall case casualty rate over all communities is 4.9% [1].

"Corona" freely signifying as "halo" or "crown" in Latin alludes to the structure seen by the capsid and RNA. "Corona virus" was really named during the imaging of the viral family Coronaviridae, because of the round state of the virus itself. Covid-19 is brought about by the novel strain of Corona virus named as SARS-CoV-2 because of its homology with SARS disease and has been proclaimed as a pandemic by the WHO (World Health Organization) on March 2020 [2]. More than 100 years since the episode of the 1918 flu pandemic, we currently appear to confront another pandemic. The episode of the new Coronavirus (SARS-CoV-2) contamination is spreading to every continent, constraining us to live with this virus for maybe quite a while. Researchers and clinicians have learned quite a bit about Covid-19, and its pathogenesis. Among more than 1000 patients investigated in Wuhan, with the exception of at times in children and adolescence, it contaminates the various age groups equitably. About 15% of the affirmed cases progress to the serious stage, despite the fact that there is a higher possibility for patients more than 65 to advance into the extreme phase [3]. SARS-CoV-2 causes intense respiratory contamination with shifting seriousness in various age groups, wherein old in general will have serious disease, in children it is moderately spread till-date [4]. Several distinctions in the pathogenesis of Covid-19 among children and adults have been proposed to clarify these differences [5]. It has been seen that less children contract Covid-19 and among infected, children have less

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serious disease [6]. In this way it is similarly critical to realize that why some evolve with serious disease, while others don't, with the goal that proposal in regards to therapeutics and when accessible, immunizations can be made. Henceforth, this review will highlight the clinical features, disease pathogenesis, age-dependent difference in immune responses among old-age and children, and immunological strategies to reduce viral burden.

Clinical Features and Outcomes of Covid-19 among Pediatric and Geriatric Patients

Among 44,762 research center affirmed cases from China, just 416 (1%) and 549 (1%) were from age-groups<10 and 10 – 19 y, respectively [4]. Similarly, out of 32,437 positive lab tests from general wellbeing labs in the United States of America (USA), 168 (0.5%) and 425 (1.3%) were the 0 – 4 and 5 – 17 years age-groups, separately. Test positivity rates among all out tests were 3.9% and 6.3% in 0 – 4 year and 5 – 17 year age groups contrasted with by and large 14.4% inspiration rates [7]. Clinical highlights from the biggest arrangement of pediatric and geriatric patients are summed up in Table 1. Recurrence of regular manifestations was lower in children and contrasting in elderly patients, suggesting more asymptomatic contaminations in children. Middle term of fever in children was 3 d contrasted with 10 d in elderly patients, suggesting shorter ailment in children. The Chinese case arrangement of 171 research center affirmed youngsters likewise announced one death in a 10-mo-old child, who endured intussusception and multi-organ failure [3,8,9]. These discoveries propose that however in general pediatric patients are less influenced and have milder disease than geriatric patients, infants have more extreme sickness when compared to older children.

Immunopathogenesis

Coronavirus entry in to host cell

Coronaviruses utilizes a spiky-formed protein, S protein, to contaminate a cell by binding to the membrane of the cell. Covid-19 (SARS-CoV-2) and SARS-CoV share a receptor-binding unit whose area structure is comparable, proposing that Covid-19 (SARS-CoV-2) utilizes ACE2 receptor in people for disease. The spike protein ties to this ACE2 receptor on the host cell surface and gets squeezed inside the host cell. Studies has been directed which shows the job of a compound Furin present in the host cells, assumes an essential role in SARS-CoV-2 passage, and can be a distinctive element characterizing the seriousness of SARS-CoV-2, since it is missing in SARS-CoV. This protein initiates SARS-CoV-2 while the SARS-CoV and MERS-CoV during passage into the host cell don't experience this enacted site. Since furin is communicated in different human organs, for example, the lungs, small digestive system, and liver, the contamination in human has been believed to be enthusiastic and can be anticipated to be possibly infecting various human organs (Figure 1). This site might influence the transmission and also the strength of the virus [2].

Characteristics	Paediatric patients		Geriatric patients	
	CDC report8	Lu et al. 20209	CDC report8	Guan et al. 2020[3]
No. of patients	2572*	171	113,985*	1099
Age group, Years	<18	<16	18-16	All ages(99.1% above 15 years)
Region	USA	China	USA	China
Male	1408(53)	104(60.8)	75,450(53)#	637(58.1)
Age, Years	11(median)	-	-	47(35,58)@
Fever	163(56)	71(41.5)	7794(71)	975(88.7)
Cough	158(54)	83(48.5)	8775(80)	745(67.8)
Fatigue	-	13(7.6)	-	419(38.1)
Myalgia	66(23)	-	6713(61)	164(14.9)
Headache	81(28)	-	6335(58)	150(13.6)
Shortness of breath	39(13)	¥	4674(43)	205(18.7)
Sore throat	71(24)	-	3795(35)	153(13.9)
Rhinorrhea	21(7.2)	13(7.6)	757(6.9)	-
Diarrhea	37(13)	15(8.8)	3353(31)	42(3.8)
Nausea/Vomiting	31(11)	-	1746(16)	55(5.0)
Abdominal pain	17(5.8)	-	1329(12)	-

Data are summarized as number (%); unless specified. @ Data summarized as median (IQR). *Denominator for estimation of symptom frequency was 291 (age<18 years) and 10,944 (age 18–64 years); because details of symptoms were available for these patients only; #Includes all patients 18 years and above; ¥ 49 (28.7%) children had tachypnea on examination in hospital. (CDC) Center for Disease Control and Prevention.

Table 1: Comparison of clinical features among pediatric and geriatric patients.

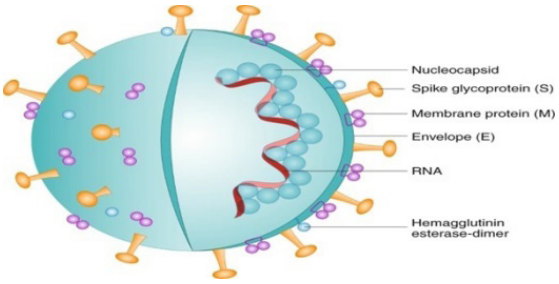

Figure 1: Schematic portrayal of SARS-CoV-2 structure. This is an encompassed, positive-sense RNA infection with four principle auxiliary proteins, including spike (S) and film (M) glycoproteins, just as envelope (E) and nucleocapsid (N) proteins.

Antigen presentation in corona virus infection

As an antiviral system Antigen presenting cells are related in the introduction of viral antigenic peptides gave major histocompatibility complex (MHC) [2] or (human leukocyte antigen (HLA) in people) and afterward distinguished by infection explicit cytotoxic T lymphocytes (CTLs). In this way the comprehension of antigen introduction of SARS-CoV-2 will assist us with gaining information on of Covid-19 pathogenesis. While there is absence of result about it or we can get just restricted data about investigations on SARS-CoV and MERS-CoV. During SARS disease, the up regulation of few chemokine's, for example, IP-10 and MP1 is seen fundamentally, additionally not many of the antiviral cytokines are seen as low in expression, for example, IFN-alpha, IFN-beta, and IFN-gamma, and TNF-alpha and IL-6 are seen as at moderate up regulation [10]. Modulation of Toll-like receptors from TLR-1 to TLR-10 apparently was at a similar level; thus no modulation but chemokine receptors, for example, CCR5, CCR3, and CCR1 are seen as at critical degree of up regulation [11]. Altogether, antigen occurrence in case of MERS-CoV-contaminated dendritic cells apparently is fundamentally higher than in SARS-CoV infected dendritic cells.

The antigen occurrence of SARS-CoV fundamentally depends on MHC I molecule however MHC II additionally added to its occurrence. HLA polymorphism alleles are concentrated on account of SARS-CoV contamination and have been isolated into susceptible alleles (HLA-B*4601, HLA-Cw*0801, HLA-B*0703, HLA-DRB1*1202) and protective alleles (HLA-DR0301, HLA-A*0201, HLA-Cw1502)4. In MERS-CoV disease MHC II molecule, for example, HLA-DQB1*02:0 and HLA-DRB1*11:01 are associated with the vulnerability to MERS-CoV contamination. Other than quality polymorphisms of mannose restricting lectin associated with antigen introduction are related to the danger of SARS-CoV disease. These investigations will give us significant hints to the counteraction, treatment and component of Covid-19 [12].

Humoral and cellular immunity

Antigen presentation subsequently initiates the body's humoral and "cellular immunity" which are intervened by infection specific T and B cells. Same as basic intense viral contaminations the immune response profile against SARS-CoV infection has a run of the mill example of IgG and IgM production. The SARS specific IgM antibodies vanish toward the end of week12 simultaneously the IgG counter acting agent may essentially assume a defensive job and the SARS specific IgG antibodies right off the bat are S-specific and N-specific antibodies. Contrasted with humoral reactions there are more explores on the cell insusceptibility of Coronavirus. The most recent report shows the quantity of CD4+ and CD8+T cells in the peripheral blood of SARS-CoV-2 infected patients is significantly diminished while its condition is over the top actuation as seen by high extents of CD38 (CD839.4%) and HLA-DR (CD43.47%) twofold positive divisions. Likewise the intense stage reaction in patients with SARS-CoV is associated with serious reduction of CD4+T and CD8+T cells. Regardless of whether there is no antigen CD4+ and CD8+ memory T cells can stay for a long time in a piece of SARS-CoV recovered people can do T cell multiplication DTH reaction and creation of IFN-γ. Six years after SARS-CoV disease explicit T cell memory reactions to the SARS-CoV S peptide library could even now be perceived in 14 of 23 recovered SARS patients. The particular CD8+T cells likewise show an equivalent impact on MERS-CoV freedom in mice [12]. These discoveries may give significant information to the discerning plan of antibodies against SARS-CoV-2.

Cytokine storm in Covid-19

Cytokine storm is a cascade of overstated immune reactions that can cause significant problems [2]. The report in lancet says Acute respiratory distress syndrome (ARDS) is the fundamental driver of death in Covid-19 patients. Out of the 41 SARS-CoV-2 infected patients conceded in introductory phases of the outbreak six passed on from ARDS. ARDS is the basic immune-pathological events for SARS-CoV, SARS-CoV-2 and MERS-CoV diseases. One of the fundamental component of ARDS is the cytokine storm the dangerous uncontrolled foundational provocative reaction which prompts arrival of a lot of pro-inflammatory cytokines (IFN-α, IFN-γ, IL-1β,IL-6, IL-12, IL-18, IL-33, TNF-α, TGFβ etc;) and chemokines (CCL2, CCL3, CXCL8, CXCL9, CXCL10 and so on;) by immune modulator cells in SARS-CoV infection. Same as SARS-CoV people, people with extreme MERS-CoV contamination shows expanded degrees of IL-6, IFN-α and CCL5, CXCL8, CXCL10 in serum contrasted with those with mild-moderate disease. Expanded degrees of IL-6 prompts poor outcome of patients with serious Covid-19 who are experiencing ARDS and pneumonia [13]. The cytokine storm will trigger an extreme attack by the immune system to the body causes ARDS, various organ failure and lastly prompts death in severe cases of SARS-CoV-2 disease similar to SARS-CoV and MERS-CoV infection [12].

Coronavirus immune evasion

The better survive in host cells SARS-CoV and MERS-CoV utilize various procedures to maintain a strategic distance from immune reactions. Explores had created with reports supporting the case that the family of Coronavirus are considerably able to suppress human immune responses by evading the immune detection mode actively [2]. The evolutionarily conserved microbial structures called pathogen-associated molecular patterns (PAMPs) can be distinguished by Designed Acknowledgment Receptors (PRRs). Anyway SARS-CoV and MERS-CoV can induce the production of twofold layer vesicles that need PRRs and afterward duplicate in these vesicles accordingly evading the host location of their twofold abandoned RNA. IFN-I (IFN-α and IFN-β) protectively affects SARS-CoV and MERS-CoV disease however the IFN-I pathway is inhibited in infected mice. Accessory protein 4a of MERS-CoV may obstruct the acceptance of IFN at the degree of MDA5 activation through direct communication with twofold abandoned RNA. Other than ORF4a, ORF4b, ORF5 and layer proteins of MERS-CoV hinder nuclear transport of IFN Regulatory Factor3 (IRF3) and activation of IFNβ promoter. The antigen introduction can also be influenced by the Coronavirus. For example gene expression related to antigen presentation is down regulated after MERS-CoV infection (Figure 2). Therefore devastating the immune evasion of SARS-CoV-2 is significant in its treatment and specific medication development [12].

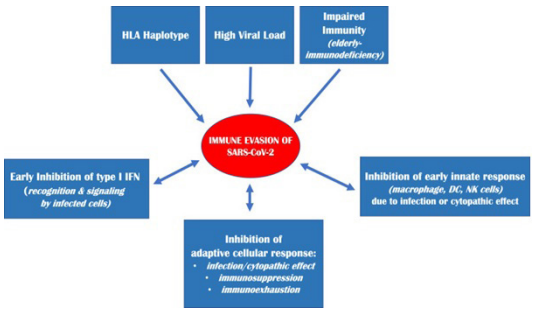

Figure 2: Possible mechanisms of immune evasion of SARS-CoV-2. Immune evasion of SARS-CoV-2 might be supported in people with compromised ability to mount efficient immune responses such as elderly people and patients with immunodeficiency or people carrying HLA alleles incapable to properly present SARSCoV-2 peptides to T lymphocytes. Moreover, a high viral load may overcome the hindrances of the immune responses. Eminently, infection escaping control may inhibit IFN-1 and infect cells of both innate and adaptive immunity by exerting a cytopathic impact. Thusly, the undermined capacity of immune cells and the hindered antiviral effect of IFN-1 would additionally support immune evasion, resulting in highly detrimental pathological impacts. (DC) Dendritic Cell.

Clinico-Immunological Stages

Clinico-immunological progression recommends that Covid-19 can be separated into 3 stages: (1) Flu like infection with high viral burden; (2) Critical stage (diminishing viral titres with quickened provocative reaction causing lung and end-organ injury); and (3) Recovery stage. SARS-CoV-2 titres in nasopharyngeal and endotracheal suction specimen are high during first seven day of symptom followed by progressive decline beginning at end of first week [14-17]. The determined high infection titres, inadequately controlled by dysfunctional immune system with raised cytokine levels, point towards consolidated impact of virus mediated cytopathic impacts and immune mediated injury as the pathway of serious lung injury and multi-organ failure during critical stage. Patients can surrender to disease during critical stage or slowly recoup. Decision of therapeutic agents varies in different stages of illness. Customized way to deal with therapeutics by setting up condition of viral burdens and provocative profile (pro- and anti-inflammatory cytokines levels) could be the best methodology. Generally, anti-viral therapy in starting phase and combination of anti-viral therapy with immunological-modulators in severe phase might be a proper choice. Early effective anti-viral medication could possibly prevent development of illness to critical phase and enhance outcomes and also intensive care burden [18].

Host Factors Affecting Individual Risk and Outcome

Poor outcomes are related with age; undoubtedly, children seem to contract SARS-CoV-2 and normally do not develop serious manifestations or complications. This is amazing as children are more prone to viral diseases including severe symptoms. Over 75% of children get exposed to occasional Coronaviruses before their fourth birthday. However, antibody titres disappear after some time, generally obvious in those more than 60 years [19]. This may diminish immune response to SARS-CoV-2 in geriatric patients as cross-reactivity between anti-occasional Coronavirus and against SARS antibodies exists, yet it adds to expanded aggravation and complexities. Immunological review impacts exist as anti-occasional Coronavirus titres increment in sera of improving SARS patients [20]. Which may impact immune pathology. In other viral diseases (for example Dengue fever), antibody dependent (ADE) permits immune cell infection and diminishes type I IFN dependent antiviral reactions while advancing pro-inflammatory IL-6 and TNF-α expression [21,22]. Another age dependent disease system might be related with live vaccinations (for example measles or BCG). Vaccines protect beyond their target antigen through induction of innate immune mechanisms termed non-specific heterologous effects. People who received BCG vaccination produce high levels of pro-inflammatory IL-1β and TNF-α in response to S. aureus or Candida spp., and BCG vaccinated infants exhibit decreased infection-related mortality [23]. ACE-2 is a counter-regulatory enzyme of renin-angiotensin system which acts by changing over angiotensin-2 to Ang-(1 – 7) structure. During good health state, ACE-2 action keep up homeostasis between angiotensin-2 (vasoconstriction, inflammation, fibrosis and proliferation) and Ang-(1 – 7) pathways (vasodilatation, anti-apoptotic, anti-fibrosis, and anti-proliferation) [18].

ACE-2 plays a vital role of transmembrane cellular receptor for SARS-CoV-2 which allows cell infection. Different ACE2 expression patterns affect disease susceptibility between tissues (e.g. respiratory epithelia Vs immune cells), but potentially also between people (men Vs women, children Vs adults) therefore determining disease progression and outcomes. Recently, it has been proposed that ACE2 expression is more in children and young women, that its expression diminishes/reduced with age, and is least in people with chronic disease, including diabetes and hypertension, inversely correlating with risk for severe disease and unfavorable outcomes. While ACE2 encourages viral entry into cells, additionally it also plays a role in controlling infection and inflammation. "ACE2 is part of the ACE2/angiotensin-(1 – 7)/MAS system as it counteracts the pro-inflammatory effects of the angiotensin-2. It catalyzes angiotensin-2 processing into angiotensin-1-7, which counteracts vasoconstriction, modulates leukocyte migration, cytokine expression, and fibrogenic pathways [24-26]. Thus, ACE2 contributes to limiting tissue inflammation while favouring repair mechanisms. Furthermore, high ACE2 expression may be of benefit as SARSCoV2 virus particles may compete with angiotensin-2 for cell surface binding sites and cellular uptake". Therefore, relatively increased ACE2 expression would clarify age-dependent difference in immune responses between children and young adults, mainly young women, are relatively protected from Covid-19 and related complications. Taken together, novel Coronaviruses, for example SARS-CoV-2, may adequately suppress early T1IFN responses, which adds to uncontrolled virus replication resulting in delayed and potentially increased cytokine responses at later stages. Early and adequate control of virus replication and micro-organism clearance might be modified in people at risk, for example the older, patients with diabetes or metabolic syndrome and so forth. Children and young people with good health may successfully control viral burden at beginning phases of infection and less frequently develop severe disease and life-threatening complications. Finally, early antibody production may result in integration of viable virus into immune cells and increased viral replication, resulting in immune complex mediated pathology, which may add to pathology in young individual with no obvious risk factors [27].

Immunological Approaches to Reduce Viral Burden

After a decade of exploration on Coronavirus, shockingly, still there are no authorized vaccines, powerful specific antivirals, nor did any drug combinations support by high-level evidence to treat the virus, particularly for recently rising strains for example, SARS-COV-2. The infected individuals are now managed mainly by giving supportive treatments, mixed low dose systematic corticosteroids, anti-viral and atomization inhalation of interferon has been advised as therapeutic option for management of severely infected Covid-19 individual [28]. Here we mainly focus on immune based treatments which may reduce virus burden.

Monoclonal and polyclonal antibodies targeting cov

Biologic medications made out of monoclonal antibodies (mAbs) have been created for treatment of an assortment of infections. A human IgG1 mAb, CR3022, that ties to SARS-CoVS protein has been developed [29] Sui et al. discovered one recombinant human mAb (single-chain variable region fragment, scFv, 80R) against the S1 domain of S protein of SARS-CoV from two nonimmune human counter acting agent libraries. The mAb could effectively neutralize SARS-CoV and block syncytia arrangement between cells communicating S protein and those communicating the SARS-CoV receptor ACE2 [30]. These neutralizing antibodies can possibly be utilized for prophylaxis for or treatment of SARS-CoV-2 disease. Agents that straightforwardly hinder the binding of S protein to the functional receptor ACE2 additionally can possibly be utilized for anticipation of Covid-19. Guillon et al. exhibited that binding of SARS-CoV S protein to ACE2 could be inhibited by anti-histo-blood group antibodies, apparently because virus carries histo-blood group antigen structures of the host [31].

Convalescent plasma

Presently, there are no any specific antiviral agents approved to novel virus therefore the use of passive antibody therapy for Covid-19 makes sense, as it's available immediately and can be tried on individuals. Proof shows that convalescent plasma therapy possesses a significant therapeutic effect and is related with lower risk in the management of severe Covid-19 patients. Studies shows that single dose of convalescent plasma with adequate amount of neutralizing antibodies decreases the viral load rapidly and enhance clinical outcomes [30].

Interferons

Interferons (IFNs), including IFN-α and IFN-β, are produced during the innate immune response to virus infection and they are able to block the replication of virus in vitro [32]. Recombinant IFN-α allowed on 3 days before the infection could decrease the viral replication and lung damage, as compared with the control in monkeys and in a pilot clinical trial [33]. The inhalation of IFN-α can be considered also the combination of interferon-α-2a with ribavirin was used in management of individual with severe MERS-CoV infection and the survival of these individual was improved [34]. These discoveries recommend that these FDA-affirmed IFN's could be utilized for the treatment of Covid-19.

Cytokine blockers

Increased virus titter and the subsequent strong inflammatory cytokine and chemokine responses are identified with the high morbidity and mortality observed during the pathogenic HCoV infection. The experience from treating SARS and MERS shows that reducing viral load through interventions in the beginning phages of the disease and controlling inflammatory responses through immune modulators are powerful measures to improve the prognosis of HCoV infection [35].

Consequently, neutralization of some of the significant cytokines is considered as a novel methodology for treatment of seriously ill patients and reducing morbidity and mortality. "Huang C et al. detailed that expanded IL-1ß, IFN-γ, IP-10, and MCP-1 in SARS-CoV-2 infection and higher concentrations of G-CSF, IP-10, MCP-1, MIP-1A, and TNF-α were found in individuals requiring medication at ICU than those not treated at ICU [36]. They additionally noticed that cytokine storm was related with disease severity. Conti et al. revealed that pro-inflammatory cytokines of interleukin (IL)-1β and IL-6 in mild and acute respiratory syndrome are associated with development of lung fibrosis in Covid-19. Therefore, suppression of pro-inflammatory IL-1 family members and IL-6 may have a potential therapeutic effect. IL-37, an immunosuppressive cytokine, acts on mTOR and expands the activity of adenosine mono-phosphate kinase, which inhibits inflammation by suppressing production of multiple cytokines downstream of My D88, including IL-1β, IL-6, TNF and CCL2. IL-37 might be a potential therapeutic cytokine for inhibition of inflammation in Covid-19" [37].

Conclusion

Covid-19 is caused by the novel strain of Coronavirus named as SARS-CoV-2 due to its homology with SARS infection and has been Proclaimed as a pandemic by the WHO (World Health Organization) on March 2020. SARS-CoV-2 causes acute respiratory infection with varying severity in different age groups, where in old-age tend to have severe disease while children are relatively saved till-date. Several differences in the pathogenesis of Covid-19 between pediatric and geriatric patients have been proposed to explain these differences. Severe Covid-19 disease is associated with high and persistent viral burden in geriatric patients. Children have strong innate immune response due to trained immunity (secondary to live-vaccines and frequent viral infections), leading to early control of infection at the site of entry and also the risk factors associated with pediatric patients were very less as compared to geriatric patients. The expression of primary target receptor for SARS-CoV-2, i.e. angiotensin converting enzyme-2 (ACE-2), decreases with age which has lung protective effects and severity of the SARS-CoV-2 can be explained by the presence of enzyme called Furin.

Authors' contributions

UY and AKG conceptualized the manuscript. UY, MJK and GA drafted the manuscript; SN, MDS and UY wrote and revised the manuscript. All the authors read and approved the final manuscript.

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