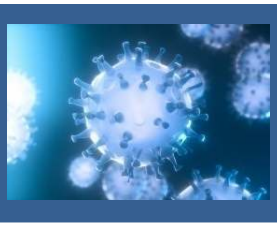
COVID-19

Jun 17 - 23, 2021



RESEARCH PUBLICATIONS

Publication Date: Jun 23, 2021

Systematic analysis of SARS-CoV-2 infection of an ACE2-negative human airway cell

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike (S) variants govern transmissibility, responsiveness to vaccination, and disease severity. In a screen for new models of SARS-CoV-2 infection, we identify human H522 lung adenocarcinoma cells as naturally permissive to SARS-CoV-2 infection despite complete absence of angiotensin-converting enzyme 2 (ACE2) expression. Remarkably, H522 infection requires the E484D S variant; viruses expressing wild-type S are not infectious. Anti-S monoclonal antibodies differentially neutralize SARS-CoV-2 E484D S in H522 cells as compared to ACE2-expressing cells. Sera from vaccinated individuals block this alternative entry mechanism, whereas convalescent sera are less effective. Although the H522 receptor remains unknown, depletion of surface heparan sulfates block H522 infection. Temporally resolved transcriptomic and proteomic profiling reveal alterations in cell cycle and the antiviral host cell response, including MDA5-dependent activation of type I interferon signaling. These findings establish an alternative SARS-CoV-2 host cell receptor for the E484D SARS-CoV-2 variant, which may impact tropism of SARS-CoV-2 and consequently human disease pathogenesis.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247%2821%2900762-2

A novel G-quadruplex aptamer-based spike trimeric antigen test for the detection of SARS-CoV-2

Abstract

Recent SARS-CoV-2 outbreak has been declared as a global health emergency. It takes years to vaccinate the whole population to protect them from this deadly virus, hence the management of SARS-CoV-2 largely depends on the widespread availability of an accurate diagnostic test. Towards addressing the unmet need of a reliable diagnostic test in the current work by utilizing the power of Systematic Evolution of Ligands by EXponential enrichment, a 44-mer G-quadruplex forming DNA aptamer against spike trimer antigen of SARS-CoV-2 was identified. The lead aptamer candidate (S14) was characterized thoroughly for its binding, selectivity, affinity, structure and batch-to-batch variability by utilizing various-biochemical, biophysical, and in silico techniques. S14 has demonstrated a low nanomolar Kd, confirming its tight binding to a spike antigen of SARS-CoV-2. S14 can detect as low as 2 nM of antigen. The clinical evaluation of S14 aptamer on nasopharyngeal swab specimens (n = 232) has displayed a highly discriminatory response between SARS-CoV-2 infected individuals from the non-infected one with a sensitivity and specificity of ~91 % and 98 %, respectively. Importantly, S14 aptamer-based test has evinced comparable performance with that of RT-PCR-based assay. Altogether, this study established the utility of aptamer technology for the detection of SARS-CoV-2.

Reference

https://www.cell.com/molecular-therapy-family/nucleic-acids/fulltext/S2162-2531%2821%2900155-4

The origins and potential future of SARS-CoV-2 variants of concern in the evolving COVID-19 pandemic

Abstract

One year into the global COVID-19 pandemic, the focus of attention has shifted to the emergence and spread of SARS-CoV-2 variants of concern (VOCs). After nearly a year of the pandemic with little evolutionary change affecting human health, several variants have now been shown to have substantial detrimental effects on transmission and

severity of the virus. Public health officials, medical practitioners, scientists, and the broader community have since been scrambling to understand what these variants mean for diagnosis, treatment, and the control of the pandemic through nonpharmaceutical interventions and vaccines. Here the evolutionary processes were explored that were involved in the emergence of new variants, what we can expect in terms of the future emergence of VOCs, and what we can do to minimise their impact.

Reference

https://www.cell.com/current-biology/fulltext/S0960-9822%2821%2900878-2

ACE2 interaction with cytoplasmic PDZ protein enhances SARS-CoV-2 invasion

Abstract

SARS-CoV-2 is responsible for the global COVID-19 pandemic. Angiotensin converting enzyme 2 (ACE2) is the membrane-delimited receptor for SARS-CoV-2. Lung, intestine, and kidney, major sites of viral infection, express ACE2 that harbors an intracellular, carboxy-terminal PDZ-recognition motif. These organs prominently express the PDZ protein Na^+/H^+ exchanger regulatory factor-1 (NHERF1). Here, we report NHERF1 tethers ACE2 and augments SARS-CoV-2 cell entry. ACE2 directly binds both NHERF1 PDZ domains. Disruption of either NHERF1 PDZ core-binding motif or the ACE2 PDZ recognition sequence eliminates interaction. Proximity ligation assays establish that ACE2 and NHERF1 interact at constitutive expression levels in human lung and intestine cells. Ablating ACE2 interaction with NHERF1 accelerated SARS-CoV-2 cell entry. Conversely, elimination of the ACE2 C-terminal PDZ-binding motif decreased ACE2 membrane residence and reduced pseudotyped virus entry. We conclude that the PDZ interaction of ACE2 with NHERF1 facilitates SARS-CoV-2 internalization. β-Arrestin is likely indispensable, as with G protein-coupled receptors.

Reference

https://www.cell.com/iscience/fulltext/S2589-0042%2821%2900738-0

Vaccine effectiveness of the first dose of ChAdOx1 nCoV-19 and BNT162b2 against SARS-CoV-2 infection in residents of long-term care facilities in England (VIVALDI): A prospective cohort study

Abstract

Background: The effectiveness of SARS-CoV-2 vaccines in older adults living in long-term care facilities is uncertain. We investigated the protective effect of the first dose of the Oxford-AstraZeneca non-replicating viral-vectored vaccine (ChAdOx1 nCoV-19; AZD1222) and the Pfizer-BioNTech mRNA-based vaccine (BNT162b2) in residents of long-term care facilities in terms of PCR-confirmed SARS-CoV-2 infection over time since vaccination.

Methods: The VIVALDI study is a prospective cohort study that commenced recruitment on June 11, 2020, to investigate SARS-CoV-2 transmission, infection outcomes, and immunity in residents and staff in long-term care facilities in England that provide residential or nursing care for adults aged 65 years and older. In this cohort study, we included long-term care facility residents undergoing routine asymptomatic SARS-CoV-2 testing between Dec 8, 2020 (the date the vaccine was first deployed in a long-term care facility), and March 15, 2021, using national testing data linked within the COVID-19 Datastore. Using Cox proportional hazards regression, we estimated the relative hazard of PCR-positive infection at 0–6 days, 7–13 days, 14–20 days, 21–27 days, 28–34 days, 35–48 days, and 49 days and beyond after vaccination, comparing unvaccinated and vaccinated person-time from the same cohort of residents, adjusting for age, sex, previous infection, local SARS-CoV-2 incidence, long-term care facility bed capacity, and clustering by long-term care facility. We also compared mean PCR cycle threshold (Ct) values for positive swabs obtained before and after vaccination. The study is registered with ISRCTN, number 14447421.

Findings: 10 412 care home residents aged 65 years and older from 310 LTCFs were included in this analysis. The median participant age was 86 years (IQR 80–91), 7247 (69·6%) of 10 412 residents were female, and 1155 residents (11·1%) had evidence of previous SARS-CoV-2 infection. 9160 (88·0%) residents received at least one vaccine dose, of whom 6138 (67·0%) received ChAdOx1 and 3022 (33·0%) received BNT162b2. Between Dec 8, 2020, and March 15, 2021, there were 36 352 PCR results

in 670 628 person-days, and 1335 PCR-positive infections (713 in unvaccinated residents and 612 in vaccinated residents) were included. Adjusted hazard ratios (HRs) for PCR-positive infection relative to unvaccinated residents declined from 28 days after the first vaccine dose to 0·44 (95% CI 0·24–0·81) at 28–34 days and 0·38 (0·19–0·77) at 35–48 days. Similar effect sizes were seen for ChAdOx1 (adjusted HR 0·32, 95% CI 0·15–0·66) and BNT162b2 (0·35, 0·17–0·71) vaccines at 35–48 days. Mean PCR Ct values were higher for infections that occurred at least 28 days after vaccination than for those occurring before vaccination (31·3 [SD 8·7] in 107 PCR-positive tests vs 26·6 [6·6] in 552 PCR-positive tests; p<0·0001).

Interpretation: Single-dose vaccination with BNT162b2 and ChAdOx1 vaccines provides substantial protection against infection in older adults from 4–7 weeks after vaccination and might reduce SARS-CoV-2 transmission. However, the risk of infection is not eliminated, highlighting the ongoing need for non-pharmaceutical interventions to prevent transmission in long-term care facilities.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00289-9/fulltext

Publication Date: Jun 22, 2021

Predication of oxygen requirement in COVID-19 patients using dynamic change of inflammatory markers: CRP, hypertension, age, neutrophil and lymphocyte (CHANeL)

Abstract

The objective of the study was to develop and validate a prediction model that identifies COVID-19 patients at risk of requiring oxygen support based on five parameters: C-reactive protein (CRP), hypertension, age, and neutrophil and lymphocyte counts (CHANeL). This retrospective cohort study included 221 consecutive COVID-19 patients and the patients were randomly assigned randomly to a training set and a test set in a ratio of 1:1. Logistic regression, logistic LASSO regression, Random Forest, Support Vector Machine, and XGBoost analyses were performed based on age, hypertension status, serial CRP, and neutrophil and lymphocyte counts during the first 3 days of hospitalization. The ability of the model to predict oxygen requirement during

hospitalization was tested. During hospitalization, 45 (41.8%) patients in the training set (n = 110) and 41 (36.9%) in the test set (n = 111) required supplementary oxygen support. The logistic LASSO regression model exhibited the highest AUC for the test set, with a sensitivity of 0.927 and a specificity of 0.814. An online risk calculator for oxygen requirement using CHANeL predictors was developed. “CHANeL” prediction models based on serial CRP, neutrophil, and lymphocyte counts during the first 3 days of hospitalization, along with age and hypertension status, provide a reliable estimate of the risk of supplement oxygen requirement among patients hospitalized with COVID-19.

Reference

https://www.nature.com/articles/s41598-021-92418-2

Structure-guided design of a perampanel-derived pharmacophore targeting the SARS-CoV-2 main protease

Abstract

There is a clinical need for direct-acting antivirals targeting SARS-CoV-2, the coronavirus responsible for the COVID-19 pandemic, to complement current therapeutic strategies. The main protease (Mpro) is an attractive target for antiviral therapy. However, the vast majority of protease inhibitors described thus far are peptidomimetic and bind to the active-site cysteine via a covalent adduct, which is generally pharmacokinetically unfavorable. The optimization of an existing FDA-approved chemical scaffold, perampanel was reported, to bind to and inhibit Mpro noncovalently with IC50s in the low-nanomolar range and EC50s in the low-micromolar range. Here, we present nine crystal structures of Mpro bound to a series of perampanel analogs, providing detailed structural insights into their mechanism of action and structure-activity relationship. These insights further reveal strategies for pursuing rational inhibitor design efforts in the context of considerable active-site flexibility and potential resistance mechanisms.

Reference

https://www.cell.com/structure/fulltext/S0969-2126%2821%2900206-9

Remote home monitoring (virtual wards) for confirmed or suspected COVID-19 patients: A rapid systematic review

Abstract

Background: The aim of this review was to analyze the implementation and impact of remote home monitoring models (virtual wards) for confirmed or suspected COVID-19 patients, identifying their main components, processes of implementation, target patient populations, impact on outcomes, costs and lessons learnt.

Methods: A rapid systematic review on models was carried out led by primary and secondary care across seven countries (US, Australia, Canada, The Netherlands, Ireland, China, UK). The main outcomes included in the review were: impact of remote home monitoring on virtual length of stay, escalation, emergency department attendance/reattendance, admission/readmission and mortality. The search was updated on February 2021. We used the PRISMA statement and the review was registered on PROSPERO (CRD: 42020202888).

Findings: The review included 27 articles. The aim of the models was to maintain patients safe in the appropriate setting. Most models were led by secondary care and confirmation of COVID-19 was not required (in most cases). Monitoring was carried via online platforms, paper-based systems with telephone calls or (less frequently) through wearable sensors. Models based on phone calls were considered more inclusive. Patient/career training was identified as a determining factor of success. We could not reach substantive conclusions regarding patient safety and the identification of early deterioration due to lack of standardized reporting and missing data. Economic analysis was not reported for most of the models and did not go beyond reporting resources used and the amount spent per patient monitored.

Interpretation: Future research should focus on staff and patient experiences of care and inequalities in patients' access to care. Attention needs to be paid to the cost-effectiveness of the models and their sustainability, evaluation of their impact on patient outcomes by using comparators, and the use of risk-stratification tools.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00245-5/fulltext

Mortality and critical care unit admission associated with the SARS-CoV-2 lineage B.1.1.7 in England: An observational cohort study

Abstract

Background: A more transmissible variant of SARS-CoV-2, the variant of concern 202012/01 or lineage B.1.1.7, has emerged in the UK. It was aimed to estimate the risk of critical care admission, mortality in patients who are critically ill, and overall mortality associated with lineage B.1.1.7 compared with non-B.1.1.7. We also compared clinical outcomes between these two groups.

Methods: For this observational cohort study, we linked large primary care (QResearch), national critical care (Intensive Care National Audit & Research Centre Case Mix Programme), and national COVID-19 testing (Public Health England) databases. SARS-CoV-2 positive samples with S-gene molecular diagnostic assay failure (SGTF) were used as a proxy for the presence of lineage B.1.1.7. We extracted two cohorts from the data: the primary care cohort, comprising patients in primary care with a positive community COVID-19 test reported between Nov 1, 2020, and Jan 26, 2021, and known SGTF status; and the critical care cohort, comprising patients admitted for critical care with a positive community COVID-19 test reported between Nov 1, 2020, and Jan 27, 2021, and known SGTF status. The associations between SARS-CoV-2 infection were explored with and without lineage B.1.1.7 and admission to a critical care unit (CCU), 28-day mortality, and 28-day mortality following CCU admission. We used Royston-Parmar models adjusted for age, sex, geographical region, other sociodemographic factors (deprivation index, ethnicity, household housing category, and smoking status for the primary care cohort; and ethnicity, body-mass index, deprivation index, and dependency before admission to acute hospital for the CCU cohort), and comorbidities (asthma, chronic obstructive pulmonary disease, type 1 and 2 diabetes, and hypertension for the primary care cohort; and cardiovascular disease, respiratory disease, metastatic disease, and immunocompromised conditions for the CCU cohort). Information on types and duration of organ support for the B.1.1.7 and non-B.1.1.7 groups were reported.

Findings: The primary care cohort included 198 420 patients with SARS-CoV-2 infection. Of these, 117 926 (59·4%) had lineage B.1.1.7, 836 (0·4%) were admitted to

CCU, and 899 (0·4%) died within 28 days. The critical care cohort included 4272 patients admitted to CCU. Of these, 2685 (62·8%) had lineage B.1.1.7 and 662 (15·5%) died at the end of critical care. In the primary care cohort, adjusted hazard ratios (HRs) of 2·15 (95% CI 1·75–2·65) were estimated for CCU admission and 1·65 (1·36–2·01) for 28-day mortality for patients with lineage B.1.1.7 compared with the non-B.1.1.7 group. The adjusted HR for mortality in critical care, estimated with the critical care cohort, was 0·91 (0·76–1·09) for patients with lineage B.1.1.7 compared with those with non-B.1.1.7 infection.

Interpretation: Patients with lineage B.1.1.7 were at increased risk of CCU admission and 28-day mortality compared with patients with non-B.1.1.7 SARS-CoV-2. For patients receiving critical care, mortality appeared to be independent of virus strain. Our findings emphasize the importance of measures to control exposure to and infection with COVID-19.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00318-2/fulltext

Risk of hospitalisation associated with infection with SARS-CoV-2 lineage B.1.1.7 in Denmark: An observational cohort study

Abstract

Background: The more infectious SARS-CoV-2 lineage B.1.1.7 rapidly spread in Europe after December, 2020, and a concern that B.1.1.7 could cause more severe disease has been raised. Taking advantage of Denmark's high RT-PCR testing and whole genome sequencing capacities, we used national health register data to assess the risk of COVID-19 hospitalisation in individuals infected with B.1.1.7 compared with those with other SARS-CoV-2 lineages.

Methods: An observational cohort study of all SARS-CoV-2-positive cases was done, and confirmed by RT-PCR in Denmark, sampled between Jan 1 and March 24, 2021, with 14 days of follow-up for COVID-19 hospitalisation. Cases were identified in the national COVID-19 surveillance system database, which includes data from the Danish Microbiology Database (RT-PCR test results), the Danish COVID-19 Genome Consortium, the National Patient Registry, the Civil Registration System, as well as

other nationwide registers. Among all cases, COVID-19 hospitalisation was defined as first admission lasting longer than 12 h within 14 days of a sample with a positive RT-PCR result. The study population and main analysis were restricted to the proportion of cases with viral genome data. The risk ratio (RR) of admission was calculated according to infection with B.1.1.7 versus other co-existing lineages with a Poisson regression model with robust SEs, adjusted a priori for sex, age, calendar time, region, and comorbidities. The contribution of each covariate to confounding of the crude RR was evaluated afterwards by a stepwise forward inclusion.

Findings: Between Jan 1 and March 24, 2021, 50 958 individuals with a positive SARS-CoV-2 test and at least 14 days of follow-up for hospitalisation were identified; 30 572 (60·0%) had genome data, of whom 10 544 (34·5%) were infected with B.1.1.7. 1944 (6·4%) individuals had a COVID-19 hospitalisation and of these, 571 (29·4%) had a B.1.1.7 infection and 1373 (70·6%) had an infection with other SARS-CoV-2 lineages. Although the overall number of hospitalisations decreased during the study period, the proportion of individuals infected with B.1.1.7 increased from 3·5% to 92·1% per week. B.1.1.7 was associated with a crude RR of hospital admission of 0·79 (95% CI 0·72–0·87; p<0·0001) and an adjusted RR of 1·42 (95% CI 1·25–1·60; p<0·0001). The adjusted RR was increased in all strata of age and calendar period—the two covariates with the largest contribution to confounding of the crude RR.

Interpretation: Infection with SARS-CoV-2 lineage B.1.1.7 was associated with an increased risk of hospitalisation compared with that of other lineages in an analysis adjusted for covariates. The overall effect on hospitalisations in Denmark was lessened due to a strict lockdown, but our findings could support hospital preparedness and modelling of the projected impact of the epidemic in countries with uncontrolled spread of B.1.1.7.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00290-5/fulltext

Chimeric spike mRNA vaccines protect against Sarbecovirus challenge in mice

Abstract

The emergence of SARS-CoV in 2003 and SARS-CoV-2 in 2019 highlights the need to develop universal vaccination strategies against the broader Sarbecovirus subgenus. Using chimeric spike designs, protection was demonstrated against challenge from SARS-CoV, SARS-CoV-2, SARS-CoV-2 B.1.351, bat CoV (Bt-CoV) RsSHC014, and a heterologous Bt-CoV WIV-1 in vulnerable aged mice. Chimeric spike mRNAs induced high levels of broadly protective neutralizing antibodies against high-risk Sarbecoviruses. In contrast, SARS-CoV-2 mRNA vaccination not only showed a marked reduction in neutralizing titers against heterologous Sarbecoviruses, but SARS-CoV and WIV-1 challenge in mice resulted in breakthrough infections. Chimeric spike mRNA vaccines efficiently neutralized D614G, mink cluster five, and the UK B.1.1.7., and South African B.1.351 variants of concern. Thus, multiplexed-chimeric spikes can prevent SARS-like zoonotic coronavirus infections with pandemic potential.

Reference

https://science.sciencemag.org/content/early/2021/06/22/science.abi4506

Drug-induced phospholipidosis confounds drug repurposing for SARS-CoV-2

Abstract

Repurposing drugs as treatments for COVID-19 has drawn much attention. Beginning with sigma receptor ligands, and expanding to other drugs from screening in the field, we became concerned that phospholipidosis was a shared mechanism underlying the antiviral activity of many repurposed drugs. For all of the 23 cationic amphiphilic drugs tested, including hydroxychloroquine, azithromycin, amiodarone, and four others already in clinical trials, phospholipidosis was monotonically correlated with antiviral efficacy. Conversely, drugs active against the same targets that did not induce phospholipidosis were not antiviral. Phospholipidosis depends on the physicochemical properties of drugs, and does not reflect specific target-based activities, rather it may be considered a toxic confound in early drug discovery. Early detection of phospholipidosis could eliminate these artifacts, enabling a focus on molecules with therapeutic potential.

Reference

https://science.sciencemag.org/content/early/2021/06/22/science.abi4708

Publication Date: Jun 21, 2021

Dysregulation of brain and choroid plexus cell types in severe COVID-19

Abstract

Although SARS-CoV-2 primarily targets the respiratory system, patients with and survivors of COVID-19 can suffer neurological symptoms. However, an unbiased understanding of the cellular and molecular processes that are affected in the brains of patients with COVID-19 is missing. Here 65,309 single-nucleus transcriptomes were profiled from 30 frontal cortex and choroid plexus samples across 14 control individuals (including 1 patient with terminal influenza) and 8 patients with COVID-19. Although our systematic analysis yields no molecular traces of SARS-CoV-2 in the brain, we observe broad cellular perturbations indicating that barrier cells of the choroid plexus sense and relay peripheral inflammation into the brain and show that peripheral T cells infiltrate the parenchyma. microglia and astrocyte subpopulations were discovered, which were associated with COVID-19 that share features with pathological cell states that have previously been reported in human neurodegenerative disease. Synaptic signalling of upper-layer excitatory neurons—which are evolutionarily expanded in humans and linked to cognitive function—is preferentially affected in COVID-19. Across cell types, perturbations associated with COVID-19 overlap with those found in chronic brain disorders and reside in genetic variants associated with cognition, schizophrenia and depression. The findings and public dataset provide a molecular framework to understand current observations of COVID-19-related neurological disease, and any such disease that may emerge at a later date.

Reference

https://www.nature.com/articles/s41586-021-03710-0

A recombinant receptor-binding domain in trimeric form generates protective immunity against SARS-CoV-2 infection in nonhuman primates

Abstract

A safe and effective vaccine is critical to combat the COVID-19 pandemic. Here, we developed a trimeric SARS-CoV-2 receptor-binding domain (RBD) subunit vaccine candidate that simulates the natural structure of the spike (S) trimer glycoprotein. Immunization with the RBD trimer-induced robust humoral and cellular immune responses, and a high level of neutralizing antibodies was maintained for at least 4.5 months. Moreover, the antibodies that were produced in response to the vaccine effectively cross-neutralized the SARS-CoV-2 501Y.V2 variant (B.1.351). Of note, when the vaccine-induced antibodies dropped to a sufficiently low level, only one boost quickly activated the anamnestic immune response, conferring full protection against a SARS-CoV-2 challenge in rhesus macaques without typical histopathological changes in the lung tissues. These results demonstrated that the SARS-CoV-2 RBD trimer vaccine candidate is highly immunogenic and safe, providing long-lasting, broad, and significant immunity protection in nonhuman primates, thereby offering an optimal vaccination strategy against COVID-19.

Reference

https://www.cell.com/the-innovation/fulltext/S2666-6758%2821%2900065-5

Isolation and characterization of cross-neutralizing coronavirus antibodies from COVID-19+ subjects

Abstract

SARS-CoV-2 is one of three coronaviruses that have crossed the animal-to-human barrier and caused widespread disease in the past two decades. The development of a universal human coronavirus vaccine could prevent future pandemics. 198 Antibodies were characterized, which were isolated from four COVID-19+ subjects and identify 14 SARS-CoV-2 neutralizing antibodies. One targets the N-terminal domain (NTD), one recognizes an epitope in S2, and 11 bind the receptor-binding domain (RBD). Three anti-RBD neutralizing antibodies cross-neutralize SARS-CoV-1 by effectively blocking binding of both the SARS-CoV-1 and SARS-CoV-2 RBDs to the ACE2 receptor. Using

the K18-hACE transgenic mouse model, it was demonstrated that the neutralization potency and antibody epitope specificity regulates the in vivo protective potential of anti-SARS-CoV-2 antibodies. All four cross-neutralizing antibodies neutralize the B.1.351 mutant strain. Thus, our study reveals that epitopes in S2 can serve as blueprints for the design of immunogens capable of eliciting cross-neutralizing coronavirus antibodies.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247%2821%2900729-4

Publication Date: Jun 18, 2021

Immunological imprinting of the antibody response in COVID-19 patients

Abstract

In addition to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), humans are also susceptible to six other coronaviruses, for which consecutive exposures to antigenically related and divergent seasonal coronaviruses are frequent. Despite the prevalence of COVID-19 pandemic and ongoing research, the nature of the antibody response against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is unclear. Here the early humoral immune response was longitudinally profiled against SARS-CoV-2 in hospitalized coronavirus disease 2019 (COVID-19) patients and quantify levels of pre-existing immunity to OC43, HKU1 and 229E seasonal coronaviruses, and find a strong back-boosting effect to conserved but not variable regions of OC43 and HKU1 betacoronaviruses spike protein. However, such antibody memory boost to human coronaviruses negatively correlates with the induction of IgG and IgM against SARS-CoV-2 spike and nucleocapsid protein. The findings thus provide evidence of immunological imprinting by previous seasonal coronavirus infections that can potentially modulate the antibody profile to SARS-CoV-2 infection.

Reference

https://www.nature.com/articles/s41467-021-23977-1

Association of social distancing and face mask use with risk of COVID-19

Abstract

Given the continued burden of COVID-19 worldwide, there is a high unmet need for data on the effect of social distancing and face mask use to mitigate the risk of COVID-19. The association of community-level social distancing measures were examined and individual face mask use with risk of predicted COVID-19 in a large prospective U.S. cohort study of 198,077 participants. Individuals living in communities with the greatest social distancing had a 31% lower risk of predicted COVID-19 compared with those living in communities with poor social distancing. Self-reported 'always' use of face mask was associated with a 62% reduced risk of predicted COVID-19 even among individuals living in a community with poor social distancing. These findings provide support for the efficacy of mask-wearing even in settings of poor social distancing in reducing COVID-19 transmission. Despite mass vaccination campaigns in many parts of the world, continued efforts at social distancing and face mask use remain critically important in reducing the spread of COVID-19.

Reference

https://www.nature.com/articles/s41467-021-24115-7

Design of COVID-19 staged alert systems to ensure healthcare capacity with minimal closures

Abstract

Community mitigation strategies to combat COVID-19, ranging from healthy hygiene to shelter-in-place orders, exact substantial socioeconomic costs. Judicious implementation and relaxation of restrictions amplify their public health benefits while reducing costs. Optimal strategies were derived for toggling between mitigation stages using daily COVID-19 hospital admissions. With public compliance, the policy triggers ensure adequate intensive care unit capacity with high probability while minimizing the duration of strict mitigation measures. In comparison, we show that other sensible COVID-19 staging policies, including France's ICU-based thresholds and a widely adopted indicator for reopening schools and businesses, require overly restrictive measures or trigger strict stages too late to avert catastrophic surges. As proof-of-

concept, the optimization and maintenance of the staged alert system were described that has guided COVID-19 policy in a large US city (Austin, Texas) since May 2020. As cities worldwide face future pandemic waves, the findings provide a robust strategy for tracking COVID-19 hospital admissions as an early indicator of hospital surges and enacting staged measures to ensure integrity of the health system, safety of the health workforce, and public confidence.

Reference

https://www.nature.com/articles/s41467-021-23989-x

Lag Time between State-level Policy Interventions and Changepoints in COVID-19 Outcomes in the United States

Abstract

State-level policy interventions have been critical in managing the spread of the new coronavirus. Here, the lag time between policy interventions and change of COVID-19 outcome trajectory in the United States, was studied. A stepwise drifts random walk model was developed to account for the non-stationarity and strong temporal correlation and subsequently apply a changepoint detection algorithm to estimate the number and times of changepoints in the COVID-19 outcome data. Furthermore, data was harmonized on the estimated changepoints with non-pharmaceutical interventions adopted by each state of the United States which provides us insights regarding the lag time between the enactment of a policy and its effect on COVID-19 outcomes. The estimated changepoints were presented for each state and the District of Columbia and find five different emerging trajectory patterns. An insight was also provided to the lag time between the enactment of a policy and its effect on COVID-19 outcomes.

Reference

https://www.cell.com/patterns/fulltext/S2666-3899%2821%2900149-5

Multi-dimensional and longitudinal systems profiling reveals predictive pattern of severe COVID-19

Abstract

COVID-19 is a respiratory tract infection that can affect multiple organ systems. Predicting the severity and clinical outcome of individual patients is a major unmet clinical need that remains challenging due to intra- and inter-patient variability. Here, more than 150 clinical, laboratory, and immunological parameters of 173 patients with mild to fatal COVID-19, were longitudinally profiled and integrated. Using systems biology, progressive dysregulation of multiple parameters were detected, which were indicative of organ damage that correlated with disease severity, particularly affecting kidneys, hepatobiliary system, and immune landscape. By performing unsupervised clustering and trajectory analysis, we identified T and B cell depletion as early indicators of a complicated disease course. In addition, markers of hepatobiliary damage emerged as robust predictor of lethal outcome in critically ill patients. This allowed us to propose a novel clinical COVID-19 SeveriTy (COST) score that distinguishes complicated disease trajectories and predicts lethal outcome in critically ill patients.

Reference

https://www.cell.com/iscience/fulltext/S2589-0042%2821%2900720-3

Ultrapotent miniproteins targeting the SARS-CoV-2 receptor-binding domain protect against infection and disease

Abstract

Despite the introduction of public health measures and spike protein-based vaccines to mitigate the COVID-19 pandemic, SARS-CoV-2 infections and deaths continue to have a global impact. Previously, a structural design approach was used to develop picomolar range miniproteins targeting the SARS-CoV-2 spike receptor-binding domain. Here, we investigated the capacity of modified versions of one lead miniprotein, LCB1, to protect against SARS-CoV-2-mediated lung disease in mice. Systemic administration of LCB1-Fc reduced viral burden, diminished immune cell infiltration and inflammation, and completely prevented lung disease and pathology. A single intranasal dose of LCB1v1.3 reduced SARS-CoV-2 infection in the lung when given as many as 5 days

before or 2 days after virus inoculation. Importantly, LCB1v1.3 protected in vivo against a historical strain (WA1/2020), an emerging B.1.1.7 strain, and a strain encoding key E484K and N501Y spike protein substitutions. These data support development of LCB1v1.3 for prevention or treatment of SARS-CoV-2 infection.

Reference

https://www.cell.com/cell-host-microbe/fulltext/S1931-3128%2821%2900286-9

***In vitro* and *in vivo* functions of SARS-CoV-2 infection-enhancing and neutralizing antibodies**

Abstract

SARS-CoV-2 neutralizing antibodies (NAbs) protect against COVID-19. A concern regarding SARS-CoV-2 antibodies is whether they mediate disease enhancement. Here, we isolated NAbs against the receptor-binding domain (RBD) and the N-terminal domain (NTD) of SARS-CoV-2 spike from individuals with acute or convalescent SARS-CoV-2 or a history of SARS-CoV infection. Cryo-electron microscopy of RBD and NTD antibodies demonstrated function-specific modes of binding. Select RBD NAbs also demonstrated Fc receptor-γ (FcγR)-mediated enhancement of virus infection in vitro, while five non-neutralizing NTD antibodies mediated FcγR-independent *in vitro* infection enhancement. However, both types of infection-enhancing antibodies protected from SARS-CoV-2 replication in monkeys and mice. Three of 46 monkeys infused with enhancing antibodies had higher lung inflammation scores compared to controls. One monkey had alveolar edema and elevated bronchoalveolar lavage inflammatory cytokines. Thus, while *in vitro* antibody-enhanced infection does not necessarily herald enhanced infection *in vivo*, increased lung inflammation can rarely occur in SARS-CoV-2 antibody-infused macaques.

Reference

https://www.cell.com/cell/fulltext/S0092-8674%2821%2900756-X

Immunogenicity of SARS-CoV-2 messenger RNA vaccines in patients with cancer

Abstract

Patients with cancer experience a higher burden of SARS-CoV-2 infection, disease severity, complications, and mortality, than the general population. SARS-CoV-2 mRNA vaccines are highly effective in the general population; however, few data are available on their efficacy in patients with cancer. Using a prospective cohort, we assessed the seroconversion rates and anti-SARS-CoV-2 spike protein antibody titers following the first and second dose of BNT162b2 and mRNA-1273 SARS-CoV-2 vaccines in patients with cancer in US and Europe from January to April 2021. Among 131 patients, most (94%) achieved seroconversion after receipt of two vaccine doses. Seroconversion rates and antibody titers in patients with hematological malignancy were significantly lower than those with solid tumors. None of the patients with history of anti-CD-20 antibody in the 6 months before vaccination developed antibody response. Antibody titers were highest for clinical surveillance or endocrine therapy groups and lowest for cytotoxic chemotherapy or monoclonal antibody groups.

Reference

https://www.cell.com/cancer-cell/fulltext/S1535-6108%2821%2900330-5

Autoimmune inflammatory rheumatic diseases and COVID-19 outcomes in South Korea: A nationwide cohort study

Abstract

Background: Real-world evidence on the association between autoimmune inflammatory rheumatic diseases, therapies related to these diseases, and COVID-19 outcomes are inconsistent. It was aimed to investigate the potential association between autoimmune inflammatory rheumatic diseases and COVID-19 early in the COVID-19 pandemic.

Methods: An exposure-driven, propensity score-matched study was done using a South Korean nationwide cohort linked to general health examination records. We analysed all South Korean patients aged older than 20 years who underwent SARS-CoV-2 RT-PCR testing between Jan 1 and May 30, 2020, and received general health examination results from the Korean National Health Insurance Service. Autoimmune inflammatory

rheumatic diseases (inflammatory arthritis and connective tissue diseases) was defined, based on the relevant ICD-10 codes, with at least two claims (outpatient or inpatient) within 1 year. The outcomes were positive SARS-CoV-2 RT-PCR test, severe COVID-19 (requirement of oxygen therapy, intensive care unit admission, application of invasive ventilation, or death), and COVID-19-related death. Adjusted odds ratios (ORs) with 95% CIs were estimated after adjusting for the potential confounders.

Findings: Between Jan 1 and May 30, 2020, 133 609 patients (70 050 [52·4%] female and 63 559 [47·6%] male) completed the general health examination and were tested for SARS-CoV-2; 4365 (3·3%) were positive for SARS-CoV-2, and 8297 (6·2%) were diagnosed with autoimmune inflammatory rheumatic diseases. After matching, patients with an autoimmune inflammatory rheumatic disease showed an increased likelihood of testing positive for SARS-CoV-2 (adjusted OR 1·19, 95% CI 1·03–1·40; p=0·026), severe COVID-19 outcomes (1·26, 1·02–1·59; p=0·041), and COVID-19-related death (1·69, 1·01–2·84; p=0·046). Similar results were observed in patients with connective tissue disease and inflammatory arthritis. Treatment with any dose of systemic corticosteroids or disease-modifying antirheumatic drugs (DMARDs) were not associated with COVID-19-related outcomes, but those receiving high dose (≥10 mg per day) of systemic corticosteroids had an increased likelihood of a positive SARS-CoV-2 test (adjusted OR 1·47, 95% CI 1·05–2·03; p=0·022), severe COVID-19 outcomes (1·76, 1·06–2·96; p=0·031), and COVID-19-related death (3·34, 1·23–8·90; p=0·017).

Interpretation: Early in the COVID-19 pandemic, autoimmune inflammatory rheumatic diseases were associated with an increased likelihood of a positive SARS-CoV-2 PCR test, worse clinical outcomes of COVID-19, and COVID-19-related deaths in South Korea. A high dose of systemic corticosteroid, but not DMARDs, showed an adverse effect on SARS-CoV-2 infection and COVID-19-related clinical outcomes.

Reference

https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(21)00151-X/fulltext

Safety and immunogenicity of the ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 in HIV infection: A single-arm sub-study of a phase 2/3 clinical trial

Abstract

Background: Data on vaccine immunogenicity against SARS-CoV-2 are needed for the 40 million people globally living with HIV who might have less functional immunity and more associated comorbidities than the general population. It was aimed to explore safety and immunogenicity of the ChAdOx1 nCoV-19 (AZD1222) vaccine in people with HIV.

Methods: In this single-arm open-label vaccination substudy within the protocol of the larger phase 2/3 trial COV002, adults aged 18–55 years with HIV were enrolled at two HIV clinics in London, UK. Eligible participants were required to be on antiretroviral therapy (ART), with undetectable plasma HIV viral loads (<50 copies per mL), and CD4 counts of more than 350 cells per μL. A prime-boost regimen of ChAdOx1 nCoV-19, with two doses was given 4–6 weeks apart. The primary outcomes for this substudy were safety and reactogenicity of the vaccine, as determined by serious adverse events and solicited local and systemic reactions. Humoral responses were measured by anti-spike IgG ELISA and antibody-mediated live virus neutralisation. Cell-mediated immune responses were measured by ex-vivo IFN-γ enzyme-linked immunospot assay (ELISpot) and T-cell proliferation. All outcomes were compared with an HIV-uninfected group from the main COV002 study within the same age group and dosing strategy and are reported until day 56 after prime vaccination. Outcomes were analysed in all participants who received both doses and with available samples. The COV002 study is registered with ClinicalTrials.gov, NCT04400838, and is ongoing.

Findings: Between Nov 5 and Nov 24, 2020, 54 participants with HIV (all male, median age 42·5 years [IQR 37·2–49·8]) were enrolled and received two doses of ChAdOx1 nCoV-19. Median CD4 count at enrolment was 694·0 cells per μL (IQR 573·5–859·5). No serious adverse events occurred. Local and systemic reactions occurring during the first 7 days after prime vaccination included pain at the injection site (26 [49%] of 53 participants with available data), fatigue (25 [47%]), headache (25 [47%]), malaise (18 [34%]), chills (12 [23%]), muscle ache (19 [36%]), joint pain (five [9%]), and nausea (four [8%]), the frequencies of which were similar to the HIV-negative participants. Anti-

spike IgG responses by ELISA peaked at day 42 (median 1440 ELISA units [EUs; IQR 704–2728]; n=50) and were sustained until day 56 (median 941 EUs [531–1445]; n=49). We found no correlation between the magnitude of the anti-spike IgG response at day 56 and CD4 cell count (p=0·93) or age (p=0·48). ELISpot and T-cell proliferative responses peaked at day 14 and 28 after prime dose and were sustained to day 56. Compared with participants without HIV, we found no difference in magnitude or persistence of SARS-CoV-2 spike-specific humoral or cellular responses (p>0·05 for all analyses).

Interpretation: In this study of people with HIV, ChAdOx1 nCoV-19 was safe and immunogenic, supporting vaccination for those well controlled on ART.

Reference

https://www.thelancet.com/journals/lanhiv/article/PIIS2352-3018(21)00103-X/fulltext

Publication Date: Jun 17, 2021

Cell-mimicking nanodecoys neutralize SARS-CoV-2 and mitigate lung injury in a non-human primate model of COVID-19

Abstract

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has grown into a global pandemic, and only a few antiviral treatments have been approved to date. Angiotensin-converting enzyme 2 (ACE2) plays a fundamental role in SARS-CoV-2 pathogenesis because it allows viral entry into host cells. Here it was shown that ACE2 nanodecoys derived from human lung spheroid cells (LSCs) can bind and neutralize SARS-CoV-2 and protect the host lung cells from infection. In mice, these LSC-nanodecoys were delivered via inhalation therapy and resided in the lungs for over 72 h post-delivery. Furthermore, inhalation of the LSC-nanodecoys accelerated clearance of SARS-CoV-2 mimics from the lungs, with no observed toxicity. In cynomolgus macaques challenged with live SARS-CoV-2, four doses of these nanodecoys delivered by inhalation promoted viral clearance and reduced lung injury. The results suggest that LSC-nanodecoys can serve as a potential therapeutic agent for treating COVID-19.

Reference

https://www.nature.com/articles/s41565-021-00923-2

BNT162b2 vaccine uptake and effectiveness in UK healthcare workers – a single centre cohort study

Abstract

In this single centre cohort study BNT162B2 vaccine uptake and effectiveness, were assessed among UK healthcare workers (HCWs) during a time of high community COVID-19 prevalence. Early uptake among HCWs was 62.3% (1409/2260), however there were significant differences in uptake between age groups, ethnic origins, and job roles. Uptake increased to 72.9% after a vaccine hesitancy working group implemented specific measures. In the 42 days after vaccination, 49 new cases of COVID-19 were identified, of which 7 (14.3%) occurred in HCWs who were beyond 10 days of vaccination. Kaplan–Meier curves for partially vaccinated and unvaccinated groups were congruent until day 14 and continued to diverge up to 42 days. Cox regression analysis showed a 70.0% (95%CI 6.0–91.0; p=0.04) risk reduction for COVID-19 infection in partially vaccinated HCWs. Here we report early vaccination rates among HCWs are generally high although uptake is lower in certain groups. It is possible to improve vaccine uptake and efforts should focus on this, however, significant resource is required. The BNT162B2 vaccine is effective from 14 days post-vaccination in a frontline clinical setting and protection continues beyond 21 days post 1st dose without a 2nd dose, being given.

Reference

https://www.nature.com/articles/s41467-021-23927-x

Antiviral effect of high-dose ivermectin in adults with COVID-19: A proof-of-concept randomized trial

Abstract

Background: There are limited antiviral options for the treatment of patients with COVID-19. Ivermectin (IVM), a macrocyclic lactone with a wide anti-parasitary spectrum, has shown potent activity against SARS-CoV-2 in vitro. This study aimed at assessing the

antiviral effect of IVM on viral load of respiratory secretions and its relationship with drug concentrations in plasma.

Methods: Proof-of-concept, pilot, randomized, controlled, outcome-assessor blinded trial to evaluate antiviral activity of high-dose IVM in 45 COVID-19 hospitalized patients randomized in a 2:1 ratio to standard of care plus oral IVM at 0·6 mg/kg/day for 5 days versus standard of care in 4 hospitals in Argentina. Eligible patients were adults with RT-PCR confirmed SARS-CoV-2 infection within 5 days of symptoms onset. The primary endpoint was the difference in viral load in respiratory secretions between baseline and day-5, by quantitative RT-PCR. Concentrations of IVM in plasma were measured. Study registered at ClinicalTrials.gov: NCT04381884.

Findings: 45 Participants were recruited (30 to IVM and 15 controls) between May 18 and September 9, 2020. There was no difference in viral load reduction between groups but a significant difference was found in patients with higher median plasma IVM levels (72% IQR 59–77) versus untreated controls (42% IQR 31–73) (p = 0·004). Mean ivermectin plasma concentration levels correlated with viral decay rate (r: 0·47, p = 0·02). Adverse events were similar between groups. No differences in clinical evolution at day-7 and day-30 between groups were observed.

Interpretation: A concentration dependent antiviral activity of oral high-dose IVM was identified at a dosing regimen that was well tolerated. Large trials with clinical endpoints are necessary to determine the clinical utility of IVM in COVID-19.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00239-X/fulltext

Influence of 25-hydroxy-cholecalciferol levels on SARS-CoV-2 infection and COVID-19 severity: A systematic review and meta-analysis

Abstract

Background: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the etiological agent of coronavirus disease 19 (COVID-19), a respiratory infection that, starting from December 2019, has spread around the world in a few months, becoming a pandemic. The lack of initial knowledge on its management has led to a great effort in developing vaccines and in finding therapeutic weapons capable of improving the

clinical outcome of the affected patients. In particular, the possible role of vitamin D status in the management of COVID-19 has been widely analysed, resulting in a great amount of data. This systematic review and meta-analysis aimed to assess whether hypovitaminosis D is a risk factor for developing SARS-CoV-2 infection and whether it affects the worsening of the clinical course of COVID-19.

Methods: Data were extracted through extensive searches in the Pubmed, MEDLINE, Cochrane, Academic One Files, Google Scholar, and Scopus databases from December 2019 to January 2021, using the keywords: “Vitamin D”, “25 hydroxy Vitamin D”, “25 hydroxycholecalciferol”, “cholecalciferol”, “COVID 19″, “SARS-CoV-2″. Observational cohort, cross-sectional, and case-control studies were included that evaluated differences in serum levels of 25-hydroxy-cholecalciferol [25(OH)D] in patients who were positive or negative for SARS-CoV-2, in patients with mild or severe forms of COVID-19, and in patients who died or were discharged from the hospital. Finally, studies that evaluated the risk of developing severe illness or death in patients with vitamin D deficiency (VDD), defined as levels of 25(OH)D <20 ng/ml, were also included. We calculated the mean difference (MD) and the 95% confidence intervals (CI) for quantitative variables such as 25(OH)D levels in patients with or without SARS-CoV-2 infection, in those with mild vs. severe COVID-19, or those who have died vs. those who have been discharged. Instead, we calculated odds ratios and 95% CI for qualitative ones, such as the number of patients with severe illness/death in the presence of VDD vs. those with normal serum 25(OH)D levels. A p-value lower than 0.05 was considered statistically significant. The study was registered on PROSPERO (CRD42021241473).

Findings: Out of 662 records, 30 articles met inclusion criteria and, therefore, were included in the meta-analysis. We found that the serum levels of 25(OH)D were significantly lower in patients with SARS-CoV-2 infection than in negative ones [MD -3.99 (-5.34, -2.64); p <0.00001; I2= 95%]. Furthermore, its levels were significantly lower in patients with severe disease [MD -6.88 (-9.74, -4.03); p <0.00001; I2=98%] and in those who died of COVID-19 [MD -8.01 (-12.50, -3.51); p = 0.0005; I2=86%]. Finally, patients with VDD had an increased risk of developing severe disease [OR 4.58 (2.24, 9.35); p <0.0001; I2=84%] but not a fatal outcome [OR 4.92 (0.83, 29.31); p = 0.08; I2=94%].

Interpretation: This meta-analysis revealed a large heterogeneity of the studies included due to the different enrolment criteria of patient samples (age, body mass index, ethnicity, comorbidities), the country where they live, all factors influencing serum 25(OH)D levels, and the different criteria used to define the severity of COVID-19. Furthermore, the observational nature of these studies does not allow to establish a cause-effect relationship, even taking into account that 25(OH)D represents a marker of acute inflammation. Treatment with vitamin D might be considered for the primary prevention of SARS-CoV-2 infection and the management of patients with COVID-19. However, further intervention studies are needed to prove this hypothesis.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00247-9/fulltext

Imatinib in patients with severe COVID-19: A randomised, double-blind, placebo-controlled, clinical trial

Abstract

Background: The major complication of COVID-19 is hypoxaemic respiratory failure from capillary leak and alveolar oedema. Experimental and early clinical data suggest that the tyrosine-kinase inhibitor imatinib reverses pulmonary capillary leak.

Methods: This randomised, double-blind, placebo-controlled, clinical trial was done at 13 academic and non-academic teaching hospitals in the Netherlands. Hospitalised patients (aged ≥18 years) with COVID-19, as confirmed by an RT-PCR test for SARS-CoV-2, requiring supplemental oxygen to maintain a peripheral oxygen saturation of greater than 94% were eligible. Patients were excluded if they had severe pre-existing pulmonary disease, had pre-existing heart failure, had undergone active treatment of a haematological or non-haematological malignancy in the previous 12 months, had cytopenia, or were receiving concomitant treatment with medication known to strongly interact with imatinib. Patients were randomly assigned (1:1) to receive either oral imatinib, given as a loading dose of 800 mg on day 0 followed by 400 mg daily on days 1–9, or placebo. Randomisation was done with a computer-based clinical data management platform with variable block sizes (containing two, four, or six patients), stratified by study site. The primary outcome was time to discontinuation of mechanical ventilation and supplemental oxygen for more than 48 consecutive hours, while being

alive during a 28-day period. Secondary outcomes included safety, mortality at 28 days, and the need for invasive mechanical ventilation. All efficacy and safety analyses were done in all randomised patients who had received at least one dose of study medication (modified intention-to-treat population). This study is registered with the EU Clinical Trials Register (EudraCT 2020–001236–10).

Findings: Between March 31, 2020, and Jan 4, 2021, 805 patients were screened, of whom 400 were eligible and randomly assigned to the imatinib group (n=204) or the placebo group (n=196). A total of 385 (96%) patients (median age 64 years [IQR 56–73]) received at least one dose of study medication and were included in the modified intention-to-treat population. Time to discontinuation of ventilation and supplemental oxygen for more than 48 h was not significantly different between the two groups (unadjusted hazard ratio [HR] 0·95 [95% CI 0·76–1·20]). At day 28, 15 (8%) of 197 patients had died in the imatinib group compared with 27 (14%) of 188 patients in the placebo group (unadjusted HR 0·51 [0·27–0·95]). After adjusting for baseline imbalances between the two groups (sex, obesity, diabetes, and cardiovascular disease) the HR for mortality was 0·52 (95% CI 0·26–1·05). The HR for mechanical ventilation in the imatinib group compared with the placebo group was 1·07 (0·63–1·80; p=0·81). The median duration of invasive mechanical ventilation was 7 days (IQR 3–13) in the imatinib group compared with 12 days (6–20) in the placebo group (p=0·0080). 91 (46%) of 197 patients in the imatinib group and 82 (44%) of 188 patients in the placebo group had at least one grade 3 or higher adverse event. The safety evaluation revealed no imatinib-associated adverse events.

Interpretation: The study failed to meet its primary outcome, as imatinib did not reduce the time to discontinuation of ventilation and supplemental oxygen for more than 48 consecutive hours in patients with COVID-19 requiring supplemental oxygen. The observed effects on survival (although attenuated after adjustment for baseline imbalances) and duration of mechanical ventilation suggest that imatinib might confer clinical benefit in hospitalised patients with COVID-19, but further studies are required to validate these findings.

Reference

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00237-X/fulltext

COMMENT

Publication Date: Jun 23, 2021

Single-dose SARS-CoV-2 vaccination efficacy in the elderly

The development of multiple successful vaccines against SARS-CoV-2 provided much-needed good news at the end of 2020. The first vaccines approved in the UK were the Pfizer–BioNTech BNT162b2 mRNA-based vaccine and the Oxford–AstraZeneca non-replicating adenoviral-vectored vaccine ChAdOx1 nCoV-19.1. Responses to single-dose vaccine were not reported in published clinical trials; however, in December, 2020, the UK Joint Committee on Vaccination and Immunisation adopted the strategy of delaying second vaccination to 12 weeks to maximise the public health impact of first-dose vaccination.

Older adults, and those with substantial comorbidity, were under-represented in vaccine trials, despite those who are frail or living in long-term care facilities having disproportionate morbidity and mortality from COVID-19. In The Lancet Infectious Diseases, two studies provide estimates of first-dose vaccine efficacy in older individuals and those living in long-term care facilities in COVID-19. These two studies report that the risk of symptomatic and asymptomatic disease substantially reduces after single-dose vaccination in groups at the highest risk of severe or fatal outcomes from COVID-19. The effect on symptomatic disease was seen from 14 days post-vaccination, and on asymptomatic disease from 28 days after vaccination. In both studies, the confidence intervals for estimates of vaccine efficacy are wide. However, these results provide reassurance that—in older adults (some of whom were frail and had many comorbidities)—both ChAdOx1 nCoV-19 and BNT162b2 provide protection from COVID-19 and, in cases of breakthrough infection, probably decrease the likelihood of viral transmission. Results from at least 42 days after vaccination will be interesting, given the UK strategy of delaying the second dose; however, these findings will be of less direct relevance for older adults in the UK given that more than 90% of people older than 65 years have now received two doses.8 These two studies give cause for optimism; despite older individuals developing decreased humoural

responses to vaccines, including SARS-CoV-2, vaccine efficacy is high, and second doses will probably increase efficacy further. We await data on clinical vaccine efficacy in other vulnerable groups, including those at risk of vaccine hyporesponsiveness, such as those with organ transplants or receiving immunosuppression. For more details, read the given link below.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00354-6/fulltext

REPORT

Publication Date: Jun 18, 2021

Ambient air pollution and low temperature associated with case fatality of COVID-19: A nationwide retrospective cohort study in China

The evidence for the effects of environmental factors on COVID-19 case fatality remains controversial, and it is crucial to understand the role of preventable environmental factors in driving COVID-19 fatality. We thus conducted a nationwide cohort study to estimate the effects of environmental factors (temperature, particulate matter [PM2.5, PM10], sulfur dioxide [SO_2], nitrogen dioxide [NO_2], and ozone [O_3]) on COVID-19 case fatality. A total of 71,808 confirmed COVID-19 cases were identified and followed up for their vital status through April 25, 2020. Exposures to ambient air pollution and temperature were estimated by linking the city- and county-level monitoring data to the residential community of each participant. For each participant, two windows were defined: the period from symptom onset to diagnosis (exposure window I) and the period from diagnosis date to date of death/recovery or end of the study period (exposure window II). Cox proportional hazards models were used to estimate the associations between these environmental factors and COVID-19 case fatality. COVID-19 case fatality increased in association with environmental factors for the two exposure windows. For example, each 10 μg/m3 increase in $PM_{2.5}$, PM_{10}, O_3, and NO_2 in window I was associated with a hazard ratio of 1.11 (95% CI 1.09, 1.13), 1.10 (95% CI 1.08, 1.13), 1.09 (95 CI 1.03, 1.14), and 1.27 (95% CI 1.19, 1.35) for COVID-19 fatality, respectively. A significant effect was also observed for low temperature, with a hazard ratio of 1.03 (95% CI 1.01, 1.04) for COVID-19 case fatality per 1°C decrease. Subgroup analysis indicated that these effects were stronger in the elderly, as well as in those with mild symptoms and living in Wuhan or Hubei. Overall, the sensitivity analyses also yielded consistent estimates. Short-term exposure to ambient air pollution and low temperature during the illness would play a nonnegligible part in causing case fatality due to COVID-19. Reduced exposures to high concentrations of $PM_{2.5}$, PM_{10}, O_3, SO_2, and NO_2 and low temperature would help improve the prognosis and reduce public health burden.

Reference

https://www.cell.com/the-innovation/fulltext/S2666-6758%2821%2900064-3