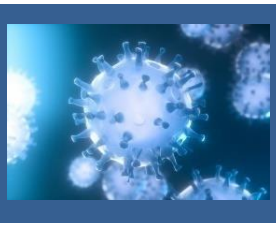
COVID-19

Aug 05 – 11, 2021



RESEARCH PUBLICATIONS

Publication Date: Aug 11, 2021

Benefit of COVID-19 vaccination accounting for potential risk compensation

Abstract

People receiving COVID-19 vaccines may subsequently markedly increase their previously suppressed exposure risk. A simple model can evaluate the benefit of vaccination to the vaccinated (index) person and others exposed to that person; and calculate the amount of risk compensation required to eliminate all the benefits or to halve the benefit. As shown, 2.5-fold increase in exposure will eliminate the benefit of a vaccine of moderate efficacy (E = 0.6) unless the probability of infection in the population of interest is very high. With very high vaccine efficacy (E = 0.95), substantial benefit is maintained except in situations where there is a very low probability of infection in the population. If the vaccine efficacy decreases to 0.8, the benefit gets eroded easily with modest risk compensation. Risk compensation may markedly affect the benefit of COVID-19 vaccination, especially if vaccine efficacy in real-life or specific high-risk populations (e.g., nursing home residents) is not very high.

Reference

https://www.nature.com/articles/s41541-021-00362-z

Mortality in individuals treated with COVID-19 convalescent plasma varies with the geographic provenance of donors

Abstract

Successful therapeutics and vaccines for coronavirus disease 2019 (COVID-19) have harnessed the immune response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Evidence that SARS-CoV-2 exists as locally evolving variants suggests

that immunological differences may impact the effectiveness of antibody-based treatments such as convalescent plasma and vaccines. Considering that near-sourced convalescent plasma likely reflects the antigenic composition of local viral strains, we hypothesize that convalescent plasma has a higher efficacy, as defined by death within 30 days of transfusion, when the convalescent plasma donor and treated patient were in close geographic proximity. Results of a series of modeling techniques applied to approximately 28,000 patients from the Expanded Access to Convalescent Plasma program (ClinicalTrials.gov number: NCT04338360) support this hypothesis. This work has implications for the interpretation of clinical studies, the ability to develop effective COVID-19 treatments, and, potentially, for the effectiveness of COVID-19 vaccines as additional locally-evolving variants continue to emerge.

Reference

https://www.nature.com/articles/s41467-021-25113-5

Therapeutic efficacy of macrolides in management of patients with mild COVID-19

Abstract

Evidence on the efficacy of adding macrolides (azithromycin or clarithromycin) to the treatment regimen for COVID-19 is limited. We testify whether adding azithromycin or clarithromycin to a standard of care regimen was superior to standard of supportive care alone in patients with mild COVID-19.This randomized trial included three groups of patients with COVID-19. The azithromycin group included, 107 patients who received azithromycin 500 mg/24 h for 7 days, the clarithromycin group included 99 patients who received clarithromycin 500 /12 h for 7 days, and the control group included 99 patients who received standard care only. All three groups received only symptomatic treatment for control of fever and cough .Clinical and biochemical evaluations of the study participants including assessment of the symptoms duration, real-time reverse transcription-polymerase chain reaction (rRT-PCR), C-reactive protein (CRP), serum ferritin, D-dimer, complete blood count (CBC), in addition to non-contrast chest computed tomography (CT), were performed. The overall results revealed significant early improvement of symptoms (fever, dyspnea and cough) in patients treated with either azithromycin or clarithromycin compared to control group, also there was significant early conversion of SARS-CoV-2 PCR to negative in patients treated with

either azithromycin or clarithromycin compared to control group ($p < 0.05$ for all).There was no significant difference in time to improvement of fever, cough, dyspnea, anosmia, gastrointestinal tract "GIT" symptoms and time to PCR negative conversion between patients treated with azithromycin compared to patients treated with clarithromycin ($p > 0.05$ for all). Follow up chest CT done after 2 weeks of start of treatment showed significant improvement in patients treated with either azithromycin or clarithromycin compared to control group ($p < 0.05$ for all).Adding Clarithromycin or azithromycin to the therapeutic protocols for COVID-19 could be beneficial for early control of fever and early PCR negative conversion in Mild COVID-19.

Reference

https://www.nature.com/articles/s41598-021-95900-z

Co-infections observed in SARS-CoV-2 positive patients using a rapid diagnostic test

Abstract

Rapid diagnostic tests are tools of paramount impact both for improving patient care and in antimicrobial management programs. Particularly in the case of respiratory infections, it is of great importance to quickly confirm/exclude the involvement of pathogens, be they bacteria or viruses, while obtaining information about the presence/absence of a genetic target of resistance to modulate antibiotic therapy. In this paper, we present our experiences with the use of the Biofire® FilmArray® Pneumonia Panel Plus (FAPP; bioMérieux; Marcy l'Etoile, France) to assess coinfection in COVID-19 patients. A total of 152 respiratory samples from consecutive patients were examined, and 93 (61%) were found to be FAPP positive, with the detection of bacteria and/or viruses. The patients were 93 males and 59 females with an average age of 65 years who were admitted to our hospital due to moderate/severe acute respiratory symptoms. Among the positive samples were 52 from sputum (SPU) and 41 from bronchoalveolar lavage (BAL). The most representative species was S. aureus (most isolates were mecA positive; 30/44, 62%), followed by gram-negative pathogens such as P. aeruginosa, K. pneumoniae, and A. baumannii. Evidence of a virus was rare. Cultures performed from BAL and SPU samples gave poor results. Most of the discrepant negative cultures were those in which FAPP detected pathogens with a

microbial count ≤ 105 CFU/mL. H. influenzae was one of the most common pathogens lost by the conventional method. Despite the potential limitations of FAPP, which detects a defined number of pathogens, its advantages of rapid detection combined with predictive information regarding the antimicrobial resistance of pathogens through the detection of some relevant markers of resistance could be very useful for establishing empirical targeted therapy for the treatment of patients with respiratory failure. In the COVID era, we understand the importance of using antibiotics wisely to curb the phenomenon of antibiotic resistance.

Reference

https://www.nature.com/articles/s41598-021-95772-3

A modified SEIR model to predict the behavior of the early stage in coronavirus and coronavirus-like outbreaks

Abstract

COVID-19 is a highly infectious disease that emerged in China at the end of 2019. The COVID-19 pandemic is the first known pandemic caused by a coronavirus, namely, the new and emerging SARS-CoV-2 coronavirus. In the present work, we present simulations of the initial outbreak of this new coronavirus using a modified transmission rate SEIR model that takes into account the impact of government actions and the perception of risk by individuals in reaction to the proportion of fatal cases. The parameters related to these effects were fitted to the number of infected cases in the 33 provinces of China. The data for Hubei Province, the probable site of origin of the current pandemic, were considered as a particular case for the simulation and showed that the theoretical model reproduces the behavior of the data, thus indicating the importance of combining government actions and individual risk perceptions when the proportion of fatal cases is greater than 4%. The results show that the adjusted model reproduces the behavior of the data quite well for some provinces, suggesting that the spread of the disease differs when different actions are evaluated. The proposed model could help to predict outbreaks of viruses with a biological and molecular structure similar to that of SARS-CoV-2.

Reference

https://www.nature.com/articles/s41598-021-95785-y

A computational study of cooperative binding to multiple SARS-CoV-2 proteins

Abstract

Structure-based drug design targeting the SARS-CoV-2 virus has been greatly facilitated by available virus-related protein structures. However, there is an urgent need for effective, safe small-molecule drugs to control the spread of the virus and variants. While many efforts are devoted to searching for compounds that selectively target individual proteins, we investigated the potential interactions between eight proteins related to SARS-CoV-2 and more than 600 compounds from a traditional Chinese medicine which has proven effective at treating the viral infection. Our original ensemble docking and cooperative docking approaches, followed by a total of over 16-micorsecond molecular simulations, have identified at least 9 compounds that may generally bind to key SARS-CoV-2 proteins. Further, we found evidence that some of these compounds can simultaneously bind to the same target, potentially leading to cooperative inhibition to SARS-CoV-2 proteins like the Spike protein and the RNA-dependent RNA polymerase. These results not only present a useful computational methodology to systematically assess the anti-viral potential of small molecules, but also point out a new avenue to seek cooperative compounds toward cocktail therapeutics to target more SARS-CoV-2-related proteins.

Reference

https://www.nature.com/articles/s41598-021-95826-6

Structure, mechanism and crystallographic fragment screening of the SARS-CoV-2 NSP13 helicase

Abstract

There is currently a lack of effective drugs to treat people infected with SARS-CoV-2, the cause of the global COVID-19 pandemic. The SARS-CoV-2 Non-structural protein 13 (NSP13) has been identified as a target for anti-virals due to its high sequence conservation and essential role in viral replication. Structural analysis reveals two

“druggable” pockets on NSP13 that are among the most conserved sites in the entire SARS-CoV-2 proteome. Here we present crystal structures of SARS-CoV-2 NSP13 solved in the APO form and in the presence of both phosphate and a non-hydrolysable ATP analog. Comparisons of these structures reveal details of conformational changes that provide insights into the helicase mechanism and possible modes of inhibition. To identify starting points for drug development we have performed a crystallographic fragment screen against NSP13. The screen reveals 65 fragment hits across 52 datasets opening the way to structure guided development of novel antiviral agents.

Reference

https://www.nature.com/articles/s41467-021-25166-6

A bagging dynamic deep learning network for diagnosing COVID-19

Abstract

COVID-19 is a serious ongoing worldwide pandemic. Using X-ray chest radiography images for automatically diagnosing COVID-19 is an effective and convenient means of providing diagnostic assistance to clinicians in practice. This paper proposes a bagging dynamic deep learning network (B-DDLN) for diagnosing COVID-19 by intelligently recognizing its symptoms in X-ray chest radiography images. After a series of preprocessing steps for images, we pre-train convolution blocks as a feature extractor. For the extracted features, a bagging dynamic learning network classifier is trained based on neural dynamic learning algorithm and bagging algorithm. B-DDLN connects the feature extractor and bagging classifier in series. Experimental results verify that the proposed B-DDLN achieves 98.8889% testing accuracy, which shows the best diagnosis performance among the existing state-of-the-art methods on the open image set. It also provides evidence for further detection and treatment.

Reference

https://www.nature.com/articles/s41598-021-95537-y

A differential equations model-fitting analysis of COVID-19 epidemiological data to explain multi-wave dynamics

Abstract

Compartmental epidemiological models are, by far, the most popular in the study of dynamics related with infectious diseases. It is, therefore, not surprising that they are frequently used to study the current COVID-19 pandemic. Taking advantage of the real-time availability of COVID-19 related data, we perform a compartmental model fitting analysis of the portuguese case, using an online open-access platform with the integrated capability of solving systems of differential equations. This analysis enabled the data-driven validation of the used model and was the basis for robust projections of different future scenarios, namely, increasing the detected infected population, reopening schools at different moments, allowing Easter celebrations to take place and population vaccination. The method presented in this work can easily be used to perform the non-trivial task of simultaneously fitting differential equation solutions to different epidemiological data sets, regardless of the model or country that might be considered in the analysis.

Reference

https://www.nature.com/articles/s41598-021-95494-6

Comparing the responses of the UK, Sweden and Denmark to COVID-19 using counterfactual modeling

Abstract

The UK and Sweden have among the worst per-capita COVID-19 mortality in Europe. Sweden stands out for its greater reliance on voluntary, rather than mandatory, control measures. We explore how the timing and effectiveness of control measures in the UK, Sweden and Denmark shaped COVID-19 mortality in each country, using a counterfactual assessment: what would the impact have been, had each country adopted the others' policies? Using a Bayesian semi-mechanistic model without prior assumptions on the mechanism or effectiveness of interventions, we estimate the time-varying reproduction number for the UK, Sweden and Denmark from daily mortality data. Two approaches were used to evaluate counterfactuals which transpose the

transmission profile from one country onto another, in each country's first wave from 13th March (when stringent interventions began) until 1st July 2020. UK mortality would have approximately doubled had Swedish policy been adopted, while Swedish mortality would have more than halved had Sweden adopted UK or Danish strategies. Danish policies were most effective, although differences between the UK and Denmark were significant for one counterfactual approach only. Our analysis shows that small changes in the timing or effectiveness of interventions have disproportionately large effects on total mortality within a rapidly growing epidemic.

Reference

https://www.nature.com/articles/s41598-021-95699-9

Altered platelet and coagulation function in moderate-to-severe COVID-19

Abstract

To reveal if coagulopathies relate to the course of COVID-19, we examined 255 patients with moderate and severe COVID-19, receiving anticoagulants and immunosuppressive drugs. Coagulopathy manifested predominantly as hypercoagulability that correlated directly with systemic inflammation, disease severity, comorbidities, and mortality risk. The prolonged clotting tests in about ¼ of cases were associated with high levels of C-reactive protein and antiphospholipid antibodies, which impeded coagulation in vitro. Contraction of blood clots was hindered in about ½ of patients, especially in severe and fatal cases, and correlated directly with prothrombotic parameters. A decrease in platelet contractility was due to moderate thrombocytopenia in combination with platelet dysfunction. Clots with impaired contraction were porous, had a low content of compressed polyhedral erythrocytes (polyhedrocytes) and an even distribution of fibrin, suggesting that the uncompacted intravital clots are more obstructive but patients could also be prone to bleeding. The absence of consumption coagulopathy suggests the predominance of local and/or regional microthrombosis rather than disseminated intravascular coagulation. The results obtained (i) confirm the importance of hemostatic disorders in COVID-19 and their relation to systemic inflammation; (ii) justify monitoring of hemostasis, including the kinetics of blood clot contraction; (iii) substantiate the active prophylaxis of thrombotic complications in COVID-19.

Reference

https://www.nature.com/articles/s41598-021-95397-6

Impact of the COVID-19 pandemic on sexual and reproductive health among women with induced abortion

Abstract

The coronavirus disease (COVID-19) has already been declared a global pandemic. To our knowledge, there is very little information regarding the effects of COVID-19 on women seeking reproductive health services, specifically abortion. This study was aimed to assess the impact of the COVID-19 pandemic on reproductive and sexual health among women seeking abortion services. A series of preliminary analyses was conducted using data collected from ten maternal and child health hospitals of seven provinces in China before and during the COVID-19 lockdown. The present study showed that a significant decrease was observed in the frequency of sexual intercourse during the COVID-19 pandemic. Moreover, a significant increase in contraceptive use including condom, rhythm method and coitus interruptus whereas a decrease in choosing oral contraceptives were observed during the COVID-19 pandemic. In addition, the pandemic was associated with increased intention of seeking induced abortion due to social factors. Future research should look into the long-term impact of the COVID-19 pandemic on sexual and reproductive health.

Reference

https://www.nature.com/articles/s41598-021-95868-w

Mechanism of molnupiravir-induced SARS-CoV-2 mutagenesis

Abstract

Molnupiravir is an orally available antiviral drug candidate currently in phase III trials for the treatment of patients with COVID-19. Molnupiravir increases the frequency of viral RNA mutations and impairs SARS-CoV-2 replication in animal models and in humans. Here, we establish the molecular mechanisms underlying molnupiravir-induced RNA mutagenesis by the viral RNA-dependent RNA polymerase (RdRp). Biochemical assays show that the RdRp uses the active form of molnupiravir, β-D-N4-hydroxycytidine (NHC) triphosphate, as a substrate instead of cytidine triphosphate or uridine triphosphate.

When the RdRp uses the resulting RNA as a template, NHC directs incorporation of either G or A, leading to mutated RNA products. Structural analysis of RdRp–RNA complexes that contain mutagenesis products shows that NHC can form stable base pairs with either G or A in the RdRp active center, explaining how the polymerase escapes proofreading and synthesizes mutated RNA. This two-step mutagenesis mechanism probably applies to various viral polymerases and can explain the broad-spectrum antiviral activity of molnupiravir.

Reference

https://www.nature.com/articles/s41594-021-00651-0

Publication Date: Aug 10, 2021

Cerebral venous thrombosis after vaccination against COVID-19 in the UK: A multicentre cohort study

Abstract

Background: A new syndrome of vaccine-induced immune thrombotic thrombocytopenia (VITT) has emerged as a rare side-effect of vaccination against COVID-19. Cerebral venous thrombosis is the most common manifestation of this syndrome but, to our knowledge, has not previously been described in detail. We aimed to document the features of post-vaccination cerebral venous thrombosis with and without VITT and to assess whether VITT is associated with poorer outcomes.

Methods: For this multicentre cohort study, clinicians were asked to submit all cases in which COVID-19 vaccination preceded the onset of cerebral venous thrombosis, regardless of the type of vaccine, interval between vaccine and onset of cerebral venous thrombosis symptoms, or blood test results. We collected clinical characteristics, laboratory results (including the results of tests for anti-platelet factor 4 antibodies where available), and radiological features at hospital admission of patients with cerebral venous thrombosis after vaccination against COVID-19, with no exclusion criteria. We defined cerebral venous thrombosis cases as VITT-associated if the lowest platelet count recorded during admission was below 150 × 109 per L and, if the D-dimer was measured, the highest value recorded was greater than 2000 μg/L. We compared the VITT and non-VITT groups for the proportion of patients who had died or were

dependent on others to help them with their activities of daily living (modified Rankin score 3–6) at the end of hospital admission (the primary outcome of the study). The VITT group were also compared with a large cohort of patients with cerebral venous thrombosis described in the International Study on Cerebral Vein and Dural Sinus Thrombosis.

Findings: Between April 1 and May 20, 2021, we received data on 99 patients from collaborators in 43 hospitals across the UK. Four patients were excluded because they did not have definitive evidence of cerebral venous thrombosis on imaging. Of the remaining 95 patients, 70 had VITT and 25 did not. The median age of the VITT group (47 years, IQR 32–55) was lower than in the non-VITT group (57 years; 41–62; p=0·0045). Patients with VITT-associated cerebral venous thrombosis had more intracranial veins thrombosed (median three, IQR 2–4) than non-VITT patients (two, 2–3; p=0·041) and more frequently had extracranial thrombosis (31 [44%] of 70 patients) compared with non-VITT patients (one [4%] of 25 patients; p=0·0003). The primary outcome of death or dependency occurred more frequently in patients with VITT-associated cerebral venous thrombosis (33 [47%] of 70 patients) compared with the non-VITT control group (four [16%] of 25 patients; p=0·0061). This adverse outcome was less frequent in patients with VITT who received non-heparin anticoagulants (18 [36%] of 50 patients) compared with those who did not (15 [75%] of 20 patients; p=0·0031), and in those who received intravenous immunoglobulin (22 [40%] of 55 patients) compared with those who did not (11 [73%] of 15 patients; p=0·022).

Interpretation: Cerebral venous thrombosis is more severe in the context of VITT. Non-heparin anticoagulants and immunoglobulin treatment might improve outcomes of VITT-associated cerebral venous thrombosis. Since existing criteria excluded some patients with otherwise typical VITT-associated cerebral venous thrombosis, we propose new diagnostic criteria that are more appropriate.

Reference

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01608-1/fulltext

Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): A randomised, controlled, open-label, adaptive platform trial

Abstract

Background: A previous efficacy trial found benefit from inhaled budesonide for COVID-19 in patients not admitted to hospital, but effectiveness in high-risk individuals is unknown. It was aimed to establish whether inhaled budesonide reduces time to recovery and COVID-19-related hospital admissions or deaths among people at high risk of complications in the community.

Methods: PRINCIPLE is a multicentre, open-label, multi-arm, randomised, controlled, adaptive platform trial done remotely from a central trial site and at primary care centres in the UK. Eligible participants were aged 65 years or older or 50 years or older with comorbidities, and unwell for up to 14 days with suspected COVID-19 but not admitted to hospital. Participants were randomly assigned to usual care, usual care plus inhaled budesonide (800 µg twice daily for 14 days), or usual care plus other interventions, and followed up for 28 days. Participants were aware of group assignment. The coprimary endpoints are time to first self-reported recovery and hospital admission or death related to COVID-19, within 28 days, analysed using Bayesian models. The primary analysis population included all eligible SARS-CoV-2-positive participants randomly assigned to budesonide, usual care, and other interventions, from the start of the platform trial until the budesonide group was closed. This trial is registered at the ISRCTN registry (ISRCTN86534580) and is ongoing.

Findings: The trial began enrolment on April 2, 2020, with randomisation to budesonide from Nov 27, 2020, until March 31, 2021, when the prespecified time to recovery superiority criterion was met. 4700 participants were randomly assigned to budesonide (n=1073), usual care alone (n=1988), or other treatments (n=1639). The primary analysis model includes 2530 SARS-CoV-2-positive participants, with 787 in the budesonide group, 1069 in the usual care group, and 974 receiving other treatments. There was a benefit in time to first self-reported recovery of an estimated 2·94 days (95% Bayesian credible interval [BCI] 1·19 to 5·12) in the budesonide group versus the usual care group (11·8 days [95% BCI 10·0 to 14·1] vs 14·7 days [12·3 to 18·0]; hazard

ratio 1·21 [95% BCI 1·08 to 1·36]), with a probability of superiority greater than 0·999, meeting the prespecified superiority threshold of 0·99. For the hospital admission or death outcome, the estimated rate was 6·8% (95% BCI 4·1 to 10·2) in the budesonide group versus 8·8% (5·5 to 12·7) in the usual care group (estimated absolute difference 2·0% [95% BCI –0·2 to 4·5]; odds ratio 0·75 [95% BCI 0·55 to 1·03]), with a probability of superiority 0·963, below the prespecified superiority threshold of 0·975. Two participants in the budesonide group and four in the usual care group had serious adverse events (hospital admissions unrelated to COVID-19).

Interpretation: Inhaled budesonide improves time to recovery, with a chance of also reducing hospital admissions or deaths (although our results did not meet the superiority threshold), in people with COVID-19 in the community who are at higher risk of complications.

Reference

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01744-X/fulltext

Effects of adjusting public health, travel, and social measures during the roll-out of COVID-19 vaccination: A modelling study

Abstract

Background: Since the emergence of the COVID-19 pandemic in late 2019, various public health and social measures (PHSMs) have been used to suppress and mitigate the spread of SARS-CoV-2. With mass vaccination programmes against COVID-19 being rolled out in many countries in early 2021, we aimed to evaluate to what extent travel restrictions and other PHSMs can be relaxed without exacerbating the local and global spread of COVID-19.

Methods: An existing age-structured susceptible-infectious-removed model of SARS-CoV-2 transmission dynamics, was adapted that can be parameterised with country-specific age demographics and contact patterns to simulate the effect of vaccination and PHSM relaxation on transmission. Assumptions were varied by age-specific susceptibility and infectiousness, vaccine uptake, contact patterns, and age structures. We used Hong Kong as a case study and assumed that, before vaccination, the population is completely susceptible to SARS-CoV-2 infection. Our model was applied

to 304 jurisdictions (27 countries and 277 sub-national administrative regions from eight countries). It was assumed that PHSMs have suppressed the effective reproductive number (Re) to fall between 1·0 and 9·0 locally before the commencement of vaccination programmes. We evaluated the levels of PHSMs that should be maintained during the roll-out of COVID-19 vaccination to avoid a large local outbreak of COVID-19, with different assumptions about vaccine efficacy, vaccination coverage, and travel restrictions. It was assumed that the maximum capacity of the health system, in terms of daily hospital admissions, is 0·005% of the population size.

Findings: At vaccine efficacy of 0·80 in reducing susceptibility to SARS-CoV-2 infection, 0·50 in reducing SARS-CoV-2 infectivity, and 0·95 in reducing symptomatic COVID-19 diseases, vaccination coverage would have to be 100% for all individuals aged 30 or older to avoid an outbreak, when relaxing PHSMs, that would overload the local health-care system, assuming a pre-vaccination Re of 2·5. Testing and quarantine of at least 5 days would have to be maintained for inbound travellers to minimise the risk of reintroducing a local outbreak until high vaccination coverages are attained locally and overseas in most countries.

Interpretation: Gradual relaxation of PHSMs should be carefully planned during the roll-out of vaccination programmes, and easing of travel restrictions weighed against risk of reintroducing outbreaks, to avoid overwhelming health systems and minimise deaths related to COVID-19.

Reference

https://www.thelancet.com/journals/lanpub/article/PIIS2468-2667(21)00167-5/fulltext

Standardized reporting systems of chest computed tomography in a population with low coronavirus disease 2019 prevalence: A retrospective comparative study

Abstract

Purpose: To compare the diagnostic performance and interobserver agreement of three reporting systems for computed tomography findings in coronavirus disease 2019 (COVID-19), namely the COVID-19 Reporting and Data System (CO-RADS), COVID-19 Imaging Reporting and Data System (COVID-RADS), and Radiological Society of North America (RSNA) expert consensus statement, in a low COVID-19 prevalence area.

Method: This institutional review board approval single-institutional retrospective study included 154 hospitalized patients between April 1 and May 21, 2020; 26 (16.9%; 63.2±14.1 years, 21 men) and 128 (65.7±16.4 years, 87 men) patients were diagnosed with and without COVID-19 according to reverse transcription-polymerase chain reaction results, respectively. Written informed consent was waived due to the retrospective nature of the study. Six radiologists independently classified chest computed tomography images according to each reporting system. The area under receiver operating characteristic curves, sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and interobserver agreements were calculated and compared across the systems using paired t-test and kappa analysis.

Results: Mean area under receiver operating characteristic curves were as follows: CO-RADS, 0.89 (95% confidence interval [CI], 0.87–0.90); COVID-RADS, 0.78 (0.75–0.80); and RSNA expert consensus statement, 0.88 (0.86–0.90). Average kappa values across observers were 0.52 (95% CI: 0.45–0.60), 0.51 (0.41–0.61), and 0.57 (0.49–0.64) for CO-RADS, COVID-RADS, and RSNA expert consensus statement, respectively. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were the highest at 0.71, 0.53, 0.72, 0.96, and 0.56 in the CO-RADS; 0.56, 0.31, 0.54, 0.95, and 0.35 in the COVID-RADS; 0.83, 0.49, 0.61, 0.96, and 0.55 in the RSNA expert consensus statement, respectively.

Conclusions: The CO-RADS exhibited the highest specificity, positive predictive value, which are especially important in a low-prevalence population, while maintaining high accuracy and negative predictive value, demonstrating the best performance in a low-prevalence population.

Reference

https://www.cell.com/heliyon/fulltext/S2405-8440(21)01846-6

Clinical validation of optimised RT-LAMP for the diagnosis of SARS-CoV-2 infection

Abstract

A reverse transcription-loop-mediated isothermal amplification (RT-LAMP) assay have optimised for the detection of SARS-CoV-2 from extracted RNA for clinical application.

The stability and reliability of the RT-LAMP assay were improved by the addition of a temperature-dependent switch oligonucleotide to reduce self- or off-target amplification. Freeze-dried master mix was then developed for single step RT-LAMP reaction, simplifying the operation for end users and improving long-term storage and transportation. The assay can detect as low as 13 copies of SARS-CoV2 RNA per reaction (25-µL). Cross reactivity with other human coronaviruses was not observed. We have applied the new RT-LAMP assay for testing clinical extracted RNA samples extracted from swabs of 72 patients in the UK and 126 samples from Greece and demonstrated the overall sensitivity of 90.2% (95% CI 83.8–94.7%) and specificity of 92.4% (95% CI 83.2–97.5%). Among 115 positive samples which Ct values were less than 34, the RT-LAMP assay was able to detect 110 of them with 95.6% sensitivity. The specificity was 100% when RNA elution used RNase-free water. The outcome of RT-LAMP can be reported by both colorimetric detection and quantifiable fluorescent reading. Objective measures with a digitized reading data flow would allow for the sharing of results for local or national surveillance.

Reference

https://www.nature.com/articles/s41598-021-95607-1

Tracking the introduction and spread of SARS-CoV-2 in coastal Kenya

Abstract

Genomic surveillance of SARS-CoV-2 is important for understanding both the evolution and the patterns of local and global transmission. Here, 311 SARS-CoV-2 genomes were generated from samples collected in coastal Kenya between 17th March and 31st July 2020. Multiple independent SARS-CoV-2 introductions were estimated into the region were primarily of European origin, although introductions could have come through neighbouring countries. Lineage B.1 accounted for 74% of sequenced cases. Lineages A, B and B.4 were detected in screened individuals at the Kenya-Tanzania border or returning travellers. Though multiple lineages were introduced into coastal Kenya following the initial confirmed case, none showed extensive local expansion other than lineage B.1. International points of entry were important conduits of SARS-CoV-2 importations into coastal Kenya and early public health responses prevented established transmission of some lineages. Undetected introductions through points of

entry including imports from elsewhere in the country gave rise to the local epidemic at the Kenyan coast.

Reference

https://www.nature.com/articles/s41467-021-25137-x

Comparative transcriptome analyses reveal genes associated with SARS-CoV-2 infection of human lung epithelial cells

Abstract

During 2020, understanding the molecular mechanism of SARS-CoV-2 infection (the cause of COVID-19) became a scientific priority due to the devastating effects of the COVID-19. Many researchers have studied the effect of this viral infection on lung epithelial transcriptomes and deposited data in public repositories. Comprehensive analysis of such data could pave the way for development of efficient vaccines and effective drugs. In the current study, high-throughput gene expression data was obtained associated with human lung epithelial cells infected with respiratory viruses such as SARS-CoV-2, SARS, H1N1, avian influenza, rhinovirus and Dhori, then performed comparative transcriptome analysis to identify SARS-CoV-2 exclusive genes. The analysis yielded seven SARS-CoV-2 specific genes including CSF2 [GM-CSF] (colony-stimulating factor 2) and calcium-binding proteins (such as S100A8 and S100A9), which are known to be involved in respiratory diseases. The analyses showed that genes involved in inflammation are commonly altered by infection of SARS-CoV-2 and influenza viruses. Furthermore, results of protein–protein interaction analyses were consistent with a functional role of CSF2 and S100A9 in COVID-19 disease. In conclusion, our analysis revealed cellular genes associated with SARS-CoV-2 infection of the human lung epithelium; these are potential therapeutic targets.

Reference

https://www.nature.com/articles/s41598-021-95733-w

Weak immunogenicity of SARS-CoV-2 vaccine in patients with hematologic malignancies

Abstract

This study evaluated the safety and immunogenicity of BNT162b2 vaccine in patients with hematological malignancies. Antibodies blocking spike binding to immobilized ACE-2 (NAb) correlated with anti-Spike (S) IgG d42 titers (Spearman $r = 0.865$, $p < 0.0001$), and an anti-S IgG d42 level ≥3100 UA/mL was predictive of NAb ≥ 30%, the positivity cutoff for NAb ($p < 0.0001$). Only 47% of the patients achieved an anti-S IgG d42 level ≥3100 UA/mL after the two BNT162b2 inocula, compared to 87% of healthy controls. In multivariable analysis, male patients, use of B-cell targeting treatment within the last 12 months prior to vaccination, and CD19+ B-cell level <120/uL, were associated with a significantly decreased probability of achieving a protective anti-S IgG level after the second BNT162b2 inoculum. Finally, using the IFN-γ ELISPOT assay, we found a significant increase in T-cell response against the S protein, with 53% of patients having an anti-S IgG-positive ELISPOT after the second BNT162b2 inoculum. There was a correlation between the anti-S ELISPOT response and IgG d42 level (Spearman $r = 0.3026$, $p = 0.012$). These findings suggest that vaccination with two BNT162b2 inocula translates into a significant increase in humoral and cellular response in patients with hematological malignancies, but only around half of the patients can likely achieve effective immune protection against COVID-19.

Reference

https://www.nature.com/articles/s41408-021-00534-z

Publication Date: Aug 09, 2021

The cytokines HGF and CXCL13 predict the severity and the mortality in COVID-19 patients

Abstract

The objective of the present study was to identify biological signatures of severe coronavirus disease 2019 (COVID-19) predictive of admission in the intensive care unit (ICU). Over 170 immunological markers were investigated in a ‘discovery’ cohort (n = 98 patients) of the Lausanne University Hospital (LUH-1). Here we report that 13 out of 49

cytokines were significantly associated with ICU admission in the three cohorts ($P < 0.05$ to $P < 0.001$), while cellular immunological markers lacked power in discriminating between ICU and non-ICU patients. The cytokine results were confirmed in two 'validation' cohorts, i.e. the French COVID-19 Study (FCS; $n = 62$) and a second LUH-2 cohort ($n = 47$). The combination of hepatocyte growth factor (HGF) and C-X-C motif chemokine ligand 13 (CXCL13) was the best predictor of ICU admission (positive and negative predictive values ranging from 81.8% to 93.1% and 85.2% to 94.4% in the 3 cohorts) and occurrence of death during patient follow-up (8.8 fold higher likelihood of death when both cytokines were increased). Of note, HGF is a pleiotropic cytokine with anti-inflammatory properties playing a fundamental role in lung tissue repair, and CXCL13, a pro-inflammatory chemokine associated with pulmonary fibrosis and regulating the maturation of B cell response. Up-regulation of HGF reflects the most powerful counter-regulatory mechanism of the host immune response to antagonize the pro-inflammatory cytokines including CXCL13 and to prevent lung fibrosis in COVID-19 patients.

Reference

https://www.nature.com/articles/s41467-021-25191-5

Inflammasome activation at the crux of severe COVID-19

Abstract

The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), results in life-threatening disease in a minority of patients, especially elderly people and those with co-morbidities such as obesity and diabetes. Severe disease is characterized by dysregulated cytokine release, pneumonia and acute lung injury, which can rapidly progress to acute respiratory distress syndrome, disseminated intravascular coagulation, multisystem failure and death. However, a mechanistic understanding of COVID-19 progression remains unclear. Here we review evidence that SARS-CoV-2 directly or indirectly activates inflammasomes, which are large multiprotein assemblies that are broadly responsive to pathogen-associated and stress-associated cellular insults, leading to secretion of the pleiotropic IL-1 family cytokines (IL-1β and IL-18), and pyroptosis, an inflammatory form of cell death. We further discuss

potential mechanisms of inflammasome activation and clinical efforts currently under way to suppress inflammation to prevent or ameliorate severe COVID-19.

Reference

https://www.nature.com/articles/s41577-021-00588-x

Progress of the COVID-19 vaccine effort: Viruses, vaccines and variants versus efficacy, effectiveness and escape

Abstract

Where 2020 saw the development and testing of vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at an unprecedented pace, the first half of 2021 has seen vaccine rollout in many countries. In this Progress article, we provide a snapshot of ongoing vaccine efficacy studies, as well as real-world data on vaccine effectiveness and the impact of virus variants of concern. Where they have been deployed in a high proportion of the adult population, the currently approved vaccines have been extremely effective in preventing COVID-19, particularly severe disease. Nonetheless, there are still significant challenges in ensuring equitable vaccine access around the globe and lessons that can be learned for controlling this pandemic and for the next pandemic.

Reference

https://www.nature.com/articles/s41577-021-00592-1

Explainable DCNN based chest X-ray image analysis and classification for COVID-19 pneumonia detection

Abstract

To speed up the discovery of COVID-19 disease mechanisms by X-ray images, this research developed a new diagnosis platform using a deep convolutional neural network (DCNN) that is able to assist radiologists with diagnosis by distinguishing COVID-19 pneumonia from non-COVID-19 pneumonia in patients based on chest X-ray classification and analysis. Such a tool can save time in interpreting chest X-rays and increase the accuracy and thereby enhance our medical capacity for the detection and diagnosis of COVID-19. The explainable method is also used in the DCNN to select

instances of the X-ray dataset images to explain the behavior of training-learning models to achieve higher prediction accuracy. The average accuracy of our method is above 96%, which can replace manual reading and has the potential to be applied to large-scale rapid screening of COVID-9 for widely use cases.

Reference

https://www.nature.com/articles/s41598-021-95680-6

Validating deep learning inference during chest X-ray classification for COVID-19 screening

Abstract

The new coronavirus unleashed a worldwide pandemic in early 2020, and a fatality rate several times that of the flu. As the number of infections soared, and capabilities for testing lagged behind, chest X-ray (CXR) imaging became more relevant in the early diagnosis and treatment planning for patients with suspected or confirmed COVID-19 infection. In a few weeks, proposed new methods for lung screening using deep learning rapidly appeared, while quality assurance discussions lagged behind. This paper proposes a set of protocols to validate deep learning algorithms, including our ROI Hide-and-Seek protocol, which emphasizes or hides key regions of interest from CXR data. Our protocol allows assessing the classification performance for anomaly detection and its correlation to radiological signatures, an important issue overlooked in several deep learning approaches proposed so far. By running a set of systematic tests over CXR representations using public image datasets, we demonstrate the weaknesses of current techniques and offer perspectives on the advantages and limitations of automated radiography analysis when using heterogeneous data sources.

Reference

https://www.nature.com/articles/s41598-021-95561-y

More than 50 long-term effects of COVID-19: A systematic review and meta-analysis

Abstract

COVID-19 can involve persistence, sequelae, and other medical complications that last weeks to months after initial recovery. This systematic review and meta-analysis aims to identify studies assessing the long-term effects of COVID-19. LitCOVID and Embase were searched to identify articles with original data published before the 1st of January 2021, with a minimum of 100 patients. For effects reported in two or more studies, meta-analyses using a random-effects model were performed using the MetaXL software to estimate the pooled prevalence with 95% CI. PRISMA guidelines were followed. A total of 18,251 publications were identified, of which 15 met the inclusion criteria. The prevalence of 55 long-term effects was estimated, 21 meta-analyses were performed, and 47,910 patients were included (age 17–87 years). The included studies defined long-COVID as ranging from 14 to 110 days post-viral infection. It was estimated that 80% of the infected patients with SARS-CoV-2 developed one or more long-term symptoms. The five most common symptoms were fatigue (58%), headache (44%), attention disorder (27%), hair loss (25%), and dyspnea (24%). Multi-disciplinary teams are crucial to developing preventive measures, rehabilitation techniques, and clinical management strategies with whole-patient perspectives designed to address long COVID-19 care.

Reference

https://www.nature.com/articles/s41598-021-95565-8

Massive surge of mRNA expression of clonal B-cell receptor in patients with COVID-19

Abstract

Background: Antibody production is one of the primary mechanisms for recovery from coronavirus disease 2019 (COVID-19). It is speculated that massive clonal expansion of B cells, which can produce clinically meaningful neutralizing antibodies, occurs in patients who recover on the timing of acquiring adaptive immunity.

Methods: To evaluate fluctuations in clonal B cells and the size of the clones, we chronologically assessed the B-cell receptor (BCR) repertoire in three patients with COVID-19 who recovered around 10 days after symptom onset.

Results: The three dominant clonotypes (top 3) were focused in each individual. The percentage frequencies of the top 3 clonotypes increased rapidly and accounted for 27.8% on day 9 in patient 1, 10.4% on day 12 in patient 2, and 10.8% on day 11 in patient 3, respectively. The frequencies of these top 3 clonotypes rapidly decreased as the patients' clinical symptoms improved. Furthermore, BCR network analysis revealed that accumulation of clusters composed of similar complementarity-determining region 3 (CDR3) sequences were rapidly formed, grew, and reached their maximum size around 10 days after symptom onset.

Conclusions: BCR repertoire analysis revealed that a massive surge of some unique BCRs occurs during the acquisition of adaptive immunity and recovery. The peaks were more prominent than expected. These results provide insight into the important role of BCRs in the recovery from COVID-19 and raise the possibility of developing neutralizing antibodies as COVID-19 immunotherapy.

Reference

https://www.cell.com/heliyon/fulltext/S2405-8440(21)01851-X

Molecular encapsulation of andrographolide in 2-hydroxypropyl-β-cyclodextrin cavity: Synthesis, characterization, pharmacokinetic and in vitro antiviral activity analysis against SARS-CoV-2

Abstract

In present investigation, AND-2-HyP-*β*-CYD (Andrographolide-2-Hydroxypropyl-*β*-cyclodextrin) complex was synthesized and characterized for antiviral and pharmacokinetic profile. The linear host-guest relation suggested synthesis of a 1:1 complex of AND with 2-HyP-*β*-CYD by inclusion mode. The Kc, stability constant of the two phase system of AND with 2-HyP-*β*-CYD computed to be 38.60×10^{-3}M. ^{1}H NMR spectrum of AND indicated the presence of triplet at 6.63-ppm which was up-fielded in AND-2-HyP-*β*-CYD complex at 6.60-ppm (doublet) confirmed the insertion of AND in cavity of 2-HyP-*β*-CYD through lactone ring. AND-2-HyP-β-CYD complex exhibited the

IC_{50} of 0.1-μg.mL^{-1} (E gene) and 0.29-μg.mL^{-1} (N gene) against SARS-CoV-2 infected Vero6 cells. Moreover, a 1.5-fold increment in extent of absorption of AND was noticed post complexation.The bioavailability was estimated to be 15.87±3.84% and 23.84±5.46%, respectively for AND and AND-2-HyP-β-CYD complex. AND-2-HyP-β-CYD complex may be a prospective candidate for further studies to evolve as a clinically viable formulation against SARS-CoV-2.

Reference

https://www.cell.com/heliyon/fulltext/S2405-8440(21)01844-2

One-shot identification of SARS-CoV-2 S RBD escape mutants using yeast screening

Abstract

The potential emergence of SARS-CoV-2 Spike (S) escape mutants is a threat to reduce the efficacy of existing vaccines and neutralizing antibody (nAb) therapies. An understanding of the antibody/S escape mutation landscape is urgently needed to preemptively address this threat. Here a rapid method was described to identify escape mutants for nAbs targeting the S receptor binding site. We identified escape mutants for five nAbs, including three from the public germline class VH3-53 elicited by natural COVID-19 infection. Escape mutations predominantly mapped to the periphery of the ACE2 recognition site on the RBD with K417, D420, Y421, F486, and Q493 as notable hotspots. Libraries, methods, and software were provided as an openly available community resource to accelerate new therapeutic strategies against SARS-CoV-2.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247(21)01065-2

Convergent antibody responses to the SARS-CoV-2 spike protein in convalescent and vaccinated individuals

Abstract

Unrelated individuals can produce genetically similar clones of antibodies, known as public clonotypes, which have been seen in responses to different infectious diseases as well as healthy individuals. Here 37 public clonotypes were identified in memory B

cells from convalescent survivors of SARS-CoV-2 infection or in plasmablasts from an individual after vaccination with mRNA-encoded spike protein. 29 Public clonotypes were identified, including clones recognizing the receptor-binding domain (RBD) in the spike protein S1 subunit (including a neutralizing, ACE2-blocking clone that protects in vivo), and others recognizing non-RBD epitopes that bound the S2 domain. Germline-revertant forms of some public clonotypes bound efficiently to spike protein, suggesting these common germline-encoded antibodies are preconfigured for avid recognition. Identification of large numbers of public clonotypes provides insight into the molecular basis of efficacy of SARS-CoV-2 vaccines and sheds light on the immune pressures driving the selection of common viral escape mutants.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247(21)01042-1

Effect of anakinra on mortality in patients with COVID-19: A systematic review and patient-level meta-analysis

Abstract

Background: Anakinra might improve the prognosis of patients with moderate to severe COVID-19 (*i.e.*, patients requiring oxygen supplementation but not yet receiving organ support). It was aimed to assess the effect of anakinra treatment on mortality in patients admitted to hospital with COVID-19.

Methods: For this systematic review and individual patient-level meta-analysis, a systematic literature search was done on Dec 28, 2020, in Medline (PubMed), Cochrane, medRxiv, bioRxiv, and the ClinicalTrials.gov databases for randomised trials, comparative studies, and observational studies of patients admitted to hospital with COVID-19, comparing administration of anakinra with standard of care, or placebo, or both. The search was repeated on Jan 22, 2021. Individual patient-level data were requested from investigators and corresponding authors of eligible studies; if individual patient-level data were not available, published data were extracted from the original reports. The primary endpoint was mortality after 28 days and the secondary endpoint was safety (eg, the risk of secondary infections). This study is registered on PROSPERO (CRD42020221491).

Findings: 209 Articles were identified, of which 178 full-text articles fulfilled screening criteria and were assessed. Aggregate data on 1185 patients from nine studies were analysed, and individual patient-level data on 895 patients were provided from six of these studies. Eight studies were observational and one was a randomised controlled trial. Most studies used historical controls. In the individual patient-level meta-analysis, after adjusting for age, comorbidities, baseline ratio of the arterial partial oxygen pressure divided by the fraction of inspired oxygen (PaO2/FiO2), C-reactive protein (CRP) concentrations, and lymphopenia, mortality was significantly lower in patients treated with anakinra (38 [11%] of 342) than in those receiving standard of care with or without placebo (137 [25%] of 553; adjusted odds ratio [OR] 0·32 [95% CI 0·20–0·51]). The mortality benefit was similar across subgroups regardless of comorbidities (ie, diabetes), ferritin concentrations, or the baseline PaO2/FiO2. In a subgroup analysis, anakinra was more effective in lowering mortality in patients with CRP concentrations higher than 100 mg/L (OR 0·28 [95% CI 0·17–0·47]). Anakinra showed a significant survival benefit when given without dexamethasone (OR 0·23 [95% CI 0·12–0·43]), but not with dexamethasone co-administration (0·72 [95% CI 0·37–1·41]). Anakinra was not associated with a significantly increased risk of secondary infections when compared with standard of care (OR 1·35 [95% CI 0·59–3·10]).

Interpretation: Anakinra could be a safe, anti-inflammatory treatment option to reduce the mortality risk in patients admitted to hospital with moderate to severe COVID-19 pneumonia, especially in the presence of signs of hyperinflammation such as CRP concentrations higher than 100 mg/L.

Reference

https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(21)00216-2/fulltext

Publication Date: Aug 08, 2021

Sensitive extraction-free SARS-CoV-2 RNA virus detection using a chelating resin

Abstract

Current conventional detection of SARS-CoV-2 involves collection of a patient sample with a nasopharyngeal swab, storage of the swab during transport in a viral transport medium, extraction of RNA, and quantitative reverse transcription PCR (RT-qPCR). We

developed a simplified preparation method using a chelating resin, Chelex, that obviates RNA extraction during viral testing. Direct detection RT-qPCR and digital-droplet PCR was compared to the current conventional method with RNA extraction for simulated samples and patient specimens. The heat-treatment in the presence of Chelex markedly improved detection sensitivity as compared to heat alone, and lack of RNA extraction shortens the overall diagnostic workflow. Furthermore, the initial sample heating step inactivates SARS-CoV-2 infectivity, thus improving workflow safety. This fast RNA preparation and detection method is versatile for a variety of samples, safe for testing personnel, and suitable for standard clinical collection and testing on high throughput platforms.

Reference

https://www.cell.com/iscience/fulltext/S2589-0042(21)00928-7

Publication Date: Aug 06, 2021

Cerebral venous thrombosis after vaccination against COVID-19 in the UK: A multicentre cohort study

Abstract

Background: A new syndrome of vaccine-induced immune thrombotic thrombocytopenia (VITT) has emerged as a rare side-effect of vaccination against COVID-19. Cerebral venous thrombosis is the most common manifestation of this syndrome but, to our knowledge, has not previously been described in detail. We aimed to document the features of post-vaccination cerebral venous thrombosis with and without VITT and to assess whether VITT is associated with poorer outcomes.

Methods: For this multicentre cohort study, clinicians were asked to submit all cases in which COVID-19 vaccination preceded the onset of cerebral venous thrombosis, regardless of the type of vaccine, interval between vaccine and onset of cerebral venous thrombosis symptoms, or blood test results. Clinical characteristics, laboratory results (including the results of tests for anti-platelet factor 4 antibodies where available), and radiological features were collected at hospital admission of patients with cerebral venous thrombosis after vaccination against COVID-19, with no exclusion criteria. We defined cerebral venous thrombosis cases as VITT-associated if the lowest

platelet count recorded during admission was below 150 × 109 per L and, if the D-dimer was measured, the highest value recorded was greater than 2000 µg/L. We compared the VITT and non-VITT groups for the proportion of patients who had died or were dependent on others to help them with their activities of daily living (modified Rankin score 3–6) at the end of hospital admission (the primary outcome of the study). The VITT group were also compared with a large cohort of patients with cerebral venous thrombosis described in the International Study on Cerebral Vein and Dural Sinus Thrombosis.

Findings: Between April 1 and May 20, 2021, data was received on 99 patients from collaborators in 43 hospitals across the UK. Four patients were excluded because they did not have definitive evidence of cerebral venous thrombosis on imaging. Of the remaining 95 patients, 70 had VITT and 25 did not. The median age of the VITT group (47 years, IQR 32–55) was lower than in the non-VITT group (57 years; 41–62; p=0·0045). Patients with VITT-associated cerebral venous thrombosis had more intracranial veins thrombosed (median three, IQR 2–4) than non-VITT patients (two, 2–3; p=0·041) and more frequently had extracranial thrombosis (31 [44%] of 70 patients) compared with non-VITT patients (one [4%] of 25 patients; p=0·0003). The primary outcome of death or dependency occurred more frequently in patients with VITT-associated cerebral venous thrombosis (33 [47%] of 70 patients) compared with the non-VITT control group (four [16%] of 25 patients; p=0·0061). This adverse outcome was less frequent in patients with VITT who received non-heparin anticoagulants (18 [36%] of 50 patients) compared with those who did not (15 [75%] of 20 patients; p=0·0031), and in those who received intravenous immunoglobulin (22 [40%] of 55 patients) compared with those who did not (11 [73%] of 15 patients; p=0·022).

Interpretation: Cerebral venous thrombosis is more severe in the context of VITT. Non-heparin anticoagulants and immunoglobulin treatment might improve outcomes of VITT-associated cerebral venous thrombosis. Since existing criteria excluded some patients with otherwise typical VITT-associated cerebral venous thrombosis, we propose new diagnostic criteria that are more appropriate.

Reference

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01608-1/fulltext

Electrocardiographic manifestations of COVID-19: Effect on cardiac activation and repolarization

Abstract

Background: Prolonged QT intervals are reported in patients with COVID-19. Additionally, virus particles in heart tissue and abnormal troponin levels have been reported. Consequently, we hypothesize that cardiac electrophysiologic abnormalities may be associated with COVID-19.

Methods: This is a retrospective study between March 15th, 2020 and May 30th, 2020 of 828 patients with COVID-19 and baseline ECG. Corrected QT (QTc) and QRS intervals were measured from ECGs performed prior to intervention or administration of QT prolonging drugs. QTc and QRS intervals were evaluated as a function of disease severity (patients admitted versus discharged; inpatients admitted to medical unit vs ICU) and cardiac involvement (troponin elevation >0.03 ng/ml, elevated B-natriuretic peptide (BNP) or NT pro-BNP >500 pg/ml). Multivariable analysis was used to test for significance. Odds ratios for predictors of disease severity and mortality were generated.

Findings: Baseline QTc of inpatients was prolonged compared to patients discharged (450.1±30.2 versus 423.4±21.7 msec, $p<0.0001$) and relative to a control group of patients with influenza ($p=0.006$). Inpatients with abnormal cardiac biomarkers had prolonged QTc and QRS compared to those with normal levels (troponin - QTc: 460.9±34.6 versus 445.3±26.6 msec, $p<0.0001$, QRS: 98.7±24.6 vs 90.5±16.9 msec, $p<0.0001$; BNP - QTc: 465.9±33.0 versus 446.0±26.2 msec, $p<0.0001$, QRS: 103.6±25.3 versus 90.6±17.6 msec, $p<0.0001$). Findings were confirmed with multivariable analysis (all $p<0.05$). QTc prolongation independently predicted mortality (8.3% increase in mortality for every 10 msec increase in QTc; OR 1.083, CI [1.002, 1.171], $p=0.04$).

Interpretation: QRS and QTc intervals are early markers for COVID-19 disease progression and mortality. ECG, a readily accessible tool, identifies cardiac involvement and may be used to predict disease course.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00337-0/fulltext

An AAV-based, room-temperature stable, single dose COVID-19 vaccine provides durable immunogenicity and protection in non-human primates

Abstract

The SARS-CoV-2 pandemic has affected more than 185 million people worldwide resulting in over 4 million deaths. To contain the pandemic, there is a continued need for safe vaccines that provide durable protection at low and scalable doses and are easily delivered. Here, AAVCOVID-1, an adeno-associated viral (AAV), Spike gene-based vaccine candidate demonstrates potent immunogenicity in mouse and nonhuman primates following a single injection and confers complete protection from SARS-CoV-2 challenge in macaques. Peak neutralizing antibody titers are sustained at 1 year and complemented by functional memory T-cell responses. The AAVCOVID vector has no relevant pre-existing immunity in humans, does not elicit cross-reactivity to common AAVs used in gene therapy, and its persistence and expression wanes following injection. The single, low dose requirement, high yield manufacturability, and 1-month stability for storage at room-temperature may make this technology well-suited to support effective immunization campaigns for emerging pathogens on a global scale.

Reference

https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(21)00378-4

Safety and immunogenicity of heterologous versus homologous prime-boost schedules with an adenoviral vectored and mRNA COVID-19 vaccine (Com-COV): A single-blind, randomised, non-inferiority trial

Abstract

Background: Use of heterologous prime-boost COVID-19 vaccine schedules could facilitate mass COVID-19 immunisation. However, It was previously reported that heterologous schedules incorporating an adenoviral vectored vaccine (ChAdOx1 nCoV-19, AstraZeneca; hereafter referred to as ChAd) and an mRNA vaccine (BNT162b2, Pfizer–BioNTech; hereafter referred to as BNT) at a 4-week interval are more

reactogenic than homologous schedules. Here, the safety and immunogenicity of heterologous schedules were reported with the ChAd and BNT vaccines.

Methods: Com-COV is a participant-blinded, randomised, non-inferiority trial evaluating vaccine safety, reactogenicity, and immunogenicity. Adults aged 50 years and older with no or well controlled comorbidities and no previous SARS-CoV-2 infection by laboratory confirmation were eligible and were recruited at eight sites across the UK. The majority of eligible participants were enrolled into the general cohort (28-day or 84-day prime-boost intervals), who were randomly assigned (1:1:1:1:1:1:1:1) to receive ChAd/ChAd, ChAd/BNT, BNT/BNT, or BNT/ChAd, administered at either 28-day or 84-day prime-boost intervals. A small subset of eligible participants (n=100) were enrolled into an immunology cohort, who had additional blood tests to evaluate immune responses; these participants were randomly assigned (1:1:1:1) to the four schedules (28-day interval only). Participants were masked to the vaccine received but not to the prime-boost interval. The primary endpoint was the geometric mean ratio (GMR) of serum SARS-CoV-2 anti-spike IgG concentration (measured by ELISA) at 28 days after boost, when comparing ChAd/BNT with ChAd/ChAd, and BNT/ChAd with BNT/BNT. The heterologous schedules were considered non-inferior to the approved homologous schedules if the lower limit of the one-sided 97·5% CI of the GMR of these comparisons was greater than 0·63. The primary analysis was done in the per-protocol population, who were seronegative at baseline. Safety analyses were done among participants receiving at least one dose of a study vaccine. The trial is registered with ISRCTN, 69254139.

Findings: Between Feb 11 and Feb 26, 2021, 830 participants were enrolled and randomised, including 463 participants with a 28-day prime-boost interval, for whom results are reported here. The mean age of participants was 57·8 years (SD 4·7), with 212 (46%) female participants and 117 (25%) from ethnic minorities. At day 28 post boost, the geometric mean concentration of SARS-CoV-2 anti-spike IgG in ChAd/BNT recipients (12 906 ELU/mL) was non-inferior to that in ChAd/ChAd recipients (1392 ELU/mL), with a GMR of 9·2 (one-sided 97·5% CI 7·5 to ∞). In participants primed with BNT, we did not show non-inferiority of the heterologous schedule (BNT/ChAd, 7133 ELU/mL) against the homologous schedule (BNT/BNT, 14 080 ELU/mL), with a GMR of

0·51 (one-sided 97·5% CI 0·43 to ∞). Four serious adverse events occurred across all groups, none of which were considered to be related to immunisation.

Interpretation: Despite the BNT/ChAd regimen not meeting non-inferiority criteria, the SARS-CoV-2 anti-spike IgG concentrations of both heterologous schedules were higher than that of a licensed vaccine schedule (ChAd/ChAd) with proven efficacy against COVID-19 disease and hospitalisation. Along with the higher immunogenicity of ChAd/BNT compared with ChAD/ChAd, these data support flexibility in the use of heterologous prime-boost vaccination using ChAd and BNT COVID-19 vaccines.

Reference

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01694-9/fulltext

Antibody development after COVID-19 vaccination in patients with autoimmune diseases in the Netherlands: A substudy of data from two prospective cohort studies

Abstract

Background: Data are scarce on immunogenicity of COVID-19 vaccines in patients with autoimmune diseases, who are often treated with immunosuppressive drugs. We aimed to investigate the effect of different immunosuppressive drugs on antibody development after COVID-19 vaccination in patients with autoimmune diseases.

Methods: In this study, serum samples were used, collected from patients with autoimmune diseases and healthy controls who were included in two ongoing prospective cohort studies in the Netherlands. Participants were eligible for inclusion in this substudy if they had been vaccinated with any COVID-19 vaccine via the Dutch national vaccine programme, which at the time was prioritising vaccination of older individuals. Samples were collected after the first or second COVID-19 vaccination. No serial samples were collected. Seroconversion rates and IgG antibody titres against the receptor-binding domain of the SARS-CoV-2 spike protein were measured. Logistic and linear regression analyses were used to investigate the association between medication use at the time of vaccination and at least until sampling, seroconversion rates, and IgG antibody titres. The studies from which data were collected are registered on the Netherlands Trial Register, Trial ID NL8513, and ClinicalTrials.org, NCT04498286.

Findings: Between April 26, 2020, and March 1, 2021, 3682 patients with rheumatic diseases, 546 patients with multiple sclerosis, and 1147 healthy controls were recruited to participate in the two prospective cohort studies. Samples were collected from patients with autoimmune diseases (n=632) and healthy controls (n=289) after their first (507 patients and 239 controls) or second (125 patients and 50 controls) COVID-19 vaccination. The mean age of both patients and controls was 63 years (SD 11), and 423 (67%) of 632 patients with autoimmune diseases and 195 (67%) of 289 controls were female. Among participants without previous SARS-CoV-2 infection, seroconversion after first vaccination were significantly lower in patients than in controls (210 [49%] of 432 patients vs 154 [73%] of 210 controls; adjusted odds ratio 0·33 [95% CI 0·23–0·48]; p<0·0001), mainly due to lower seroconversion in patients treated with methotrexate or anti-CD20 therapies. After the second vaccination, seroconversion exceeded 80% in all patient treatment subgroups, except among those treated with anti-CD20 therapies (three [43%] of seven patients). We observed no difference in seroconversion and IgG antibody titres between patients with a previous SARS-CoV-2 infection who had received a single vaccine dose (72 [96%] of 75 patients, median IgG titre 127 AU/mL [IQR 27–300]) and patients without a previous SARS-CoV-2 infection who had received two vaccine doses (97 [92%] of 106 patients, median IgG titre 49 AU/mL [17–134]).

Interpretation: The data suggest that seroconversion after a first COVID-19 vaccination is delayed in older patients on specific immunosuppressive drugs, but that second or repeated exposure to SARS-CoV-2, either *via* infection or vaccination, improves humoral immunity in patients treated with immunosuppressive drugs. Therefore, delayed second dosing of COVID-19 vaccines should be avoided in patients receiving immunosuppressive drugs. Future studies that include younger patients need to be done to confirm the generalisability of the results.

Reference

https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(21)00222-8/fulltext

Upregulation of pulmonary tissue factor, loss of thrombomodulin and immunothrombosis in SARS-CoV-2 infection

Abstract

Background: SARS-CoV-2 infection is associated with thrombotic and microvascular complications. The cause of coagulopathy in the disease is incompletely understood.

Methods: A single-center cross-sectional study including 66 adult COVID-19 patients (40 moderate, 26 severe disease), and 9 controls, performed between 04/2020 and 10/2020. Markers of coagulation, endothelial cell function [angiopoietin-1,-2, P-selectin, von Willebrand Factor Antigen (WF:Ag), von Willebrand Factor Ristocetin Cofactor, ADAMTS13, thrombomodulin, soluble Endothelial cell Protein C Receptor (sEPCR), Tissue Factor Pathway Inhibitor], neutrophil activation (elastase, citrullinated histones) and fibrinolysis (tissue-type plasminogen activator, plasminogen activator inhibitor-1) were evaluated using ELISA. Tissue Factor (TF) was estimated by antithrombin-FVIIa complex (AT/FVIIa) and microparticles-TF (MP-TF). We correlated each marker and determined its association with severity. Expression of pulmonary TF, thrombomodulin and EPCR was determined by immunohistochemistry in 9 autopsies.

Findings: Comorbidities were frequent in both groups, with older age associated with severe disease. All patients were on prophylactic anticoagulants. Three patients (4.5%) developed pulmonary embolism. Mortality was 7.5%. Patients presented with mild alterations in the coagulogram (compensated state). Biomarkers of endothelial cell, neutrophil activation and fibrinolysis were elevated in severe vs moderate disease; AT/FVIIa and MP-TF levels were higher in severe patients. Logistic regression revealed an association of D-dimers, angiopoietin-1, vWF:Ag, thrombomodulin, white blood cells, absolute neutrophil count (ANC) and hemoglobin levels with severity, with ANC and vWF:Ag identified as independent factors. Notably, postmortem specimens demonstrated epithelial expression of TF in the lung of fatal COVID-19 cases with loss of thrombomodulin staining, implying in a shift towards a procoagulant state.

Interpretation: Coagulation dysregulation has multifactorial etiology in SARS-Cov-2 infection. Upregulation of pulmonary TF with loss of thrombomodulin emerge as a potential link to immunothrombosis, and therapeutic targets in the disease.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00349-7/fulltext

Long-term SARS-CoV-2-specific immune and inflammatory responses in individuals recovering from COVID-19 with and without post-acute symptoms

Abstract

We describe severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-specific T cell responses, soluble markers of inflammation, and antibody levels and neutralization capacity longitudinally in 70 individuals with PCR-confirmed SARS-CoV-2 infection. Participants represent a spectrum of illness and recovery, including some with persistent viral shedding in saliva and many experiencing post-acute sequelae of SARS-CoV-2 infection (PASC). T cell responses remain stable for up to 9 months. Whereas the magnitude of early CD4+ T cell immune responses correlates with severity of initial infection, pre-existing lung disease is independently associated with higher long-term SARS-CoV-2-specific CD8+ T cell responses. Among participants with PASC 4 months following coronavirus disease 2019 (COVID-19) symptom onset, we observe a lower frequency of CD8+ T cells expressing CD107a, a marker of degranulation, in response to Nucleocapsid (N) peptide pool stimulation, and a more rapid decline in the frequency of N-specific interferon-γ-producing CD8+ T cells. Neutralizing antibody levels strongly correlate with SARS-CoV-2-specific CD4+ T cell responses.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247(21)00948-7

A comprehensive analysis of the efficacy and safety of COVID-19 vaccines

Abstract

The numbers of cases and deaths from coronavirus disease 2019 (COVID-19) are continuously increasing. Many people are concerned about the efficacy and safety of the COVID-19 vaccines. A comprehensive analysis of the published trials of COVID-19 vaccines was performed and the real-world data from the Vaccine Adverse Event Reporting System. Globally, our research found that the efficacy of all vaccines exceeded 70%, and RNA-based vaccines had the highest efficacy of 94.29%; moreover, Black or African American people, young people and males may experience

greater vaccine efficacy. The spectrum of vaccine-related adverse drug reactions (ADRs) is extremely broad, the most frequent ADRs are pain, fatigue and headache. Most ADRs are tolerable and are mainly grade 1 or 2 in severity. Some severe ADRs have been identified (thromboembolic events: 21-75 cases per million doses; myocarditis/pericarditis: 2-3 cases per million doses). In summary, vaccines are a powerful tool that can be used to control the COVID-19 pandemic, with high efficacy and tolerable ADRs. In addition, the spectrum of ADRs associated with the vaccines is broad, and most of the reactions appear within a week, while some may be delayed. Therefore, ADRs after vaccination need to be identified and addressed in a timely manner.

Reference

https://www.cell.com/molecular-therapy-family/molecular-therapy/fulltext/S1525-0016(21)00395-6

IN BRIEF

Publication Date: Aug 10, 2021

Poor nasal immunity can lead to severe COVID-19

The clinical picture of COVID-19 varies widely. Many SARS-CoV-2-infected individuals have upper respiratory symptoms only, indicating that local immunity can constrain viral pathology to the nasopharynx. A study in Cell by Ziegler *et al*. investigated early intrinsic immune responses by single-cell RNA-seq of nasopharyngeal swabs from 58 individuals, including 35 who were recently diagnosed with COVID-19. In patients with mild-to-moderate disease, epithelial cells expressed antiviral and interferon-responsive genes. These responses were muted in individuals with severe COVID-19, despite equivalent viral loads. Severe disease was also characterized by the mucosal recruitment of highly inflammatory myeloid populations. The authors mapped viral tropism to specific epithelial cell subsets and defined host pathways that were linked with susceptibility or resistance. Overall, their study suggests that failed nasal epithelial antiviral immunity underlies severe COVID-19 and that host responses in the nasal mucosa are an essential determinant of the overall disease trajectory.

Reference

https://www.nature.com/articles/s41577-021-00610-2