

The relationship between viral clearance rates and disease progression in early symptomatic COVID-19: a systematic review and meta-regression analysis

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Background: Effective antiviral drugs accelerate viral clearance in acute COVID-19 infections; the relationship between accelerating viral clearance and reducing severe clinical outcomes is unclear.

Methods: A systematic review was conducted of randomized controlled trials (RCTs) of antiviral therapies in early symptomatic COVID-19, where viral clearance data were available. Treatment benefit was defined clinically as the relative risk of hospitalization/death during follow-up (≥ 14 days), and virologically as the SARS-CoV-2 viral clearance rate ratio (VCRR). The VCRR is the ratio of viral clearance rates between the intervention and control arms. The relationship between the clinical and virological treatment effects was assessed by mixed-effects meta-regression.

Results: From 57 potentially eligible RCTs, VCRRs were derived for 44 (52 384 participants); 32 had ≥ 1 clinical endpoint in each arm. Overall, 9.7% (R^2) of the variation in clinical benefit was explained by variation in VCRRs with an estimated linear coefficient of -0.92 (95% CI: -1.99 to 0.13 ; $P=0.08$). However, this estimate was highly sensitive to the inclusion of the recent very large PANORAMIC trial. Omitting this outlier, half the variation in clinical benefit ($R^2=50.4\%$) was explained by variation in VCRRs [slope -1.47 (95% CI -2.43 to -0.51); $P=0.003$], i.e. higher VCRRs were associated with an increased clinical benefit.

Conclusion: Methods of determining viral clearance in COVID-19 studies and the relationship to clinical outcomes vary greatly. As prohibitively large sample sizes are now required to show clinical treatment benefit in antiviral therapeutic assessments, viral clearance is a reasonable surrogate endpoint.

Introduction

COVID-19 is characterized by rapid viral replication early in the acute infection. Progression to severe disease occurs in a minority of patients after an interval of approximately 1 week. Whereas the initial symptoms result directly from the SARS-CoV-2 burden, the later severe phase with potentially lethal pneumonitis results from immunopathogenesis.¹ Antiviral therapies are, therefore, expected to provide greatest therapeutic benefit early in the course of infection (i.e. within the first week) when viral densities are highest. Several antiviral interventions have been shown to reduce subsequent all-cause hospitalization and death.^{2–5} However, as the pandemic has evolved the incidence of these severe clinical endpoints has declined substantially. Among

COVID-19 cases referred to hospital, inflammatory viral pneumonitis, the main pathological process leading to death, is proportionally less. This now limits the ability of antiviral trials in COVID-19 to detect a treatment effect if prevention of all-cause hospitalization or death is their primary endpoint. The rate of viral clearance from the nasopharynx or oropharynx has been proposed as a surrogate endpoint in COVID-19,^{6,7} but the relationship between acceleration in viral clearance and prevention of disease progression is unclear.

In general, in infectious diseases, pathogen clearance correlates with clinical responses.⁸ Viral load reductions are established as surrogate endpoints of therapeutic efficacy in several different chronic viral infections, including HIV, Hepatitis B and C, and CMV infections in organ transplant patients.^{9–12} This is not the case for

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Infectious Disease Challenges in Solid Organ Transplant Recipients, an Issue of Infectious Disease Clinics Joseph G Timpone Jr.,Princy N. Kumar,2013-06-28 The potential etiologies of infection are diverse and these infections can often progress rapidly in SOT patients Diagnosis can be difficult owing to the altered anatomy that sometimes follows transplant surgery Many of the areas related to infections in SOT recipients are unresolved and controversial and recognized emerging issues include donor derived infection the impact of pandemic influenza in the SOT recipient and drug resistant infections

Current Progress and Challenges in the Development of a Hepatitis C Virus Vaccine Steven K.H. Fount,Thomas F. Baumert,2019-01-22 More than 70 million people worldwide are infected with hepatitis C virus a major cause of liver cirrhosis liver failure and hepatocellular carcinoma world wide In the last decade this cancer has emerged as the second leading cause of cancer death and the global burden is increasing by two million new infections per year mainly due to injection drug use An effective vaccine will be the most effective means to contain the spread of this virus worldwide The articles in this Research Topic describe the progress that has been made towards a preventive vaccine and the challenges that still need to be overcome to ultimately achieve this goal

Why Vaccines to HIV, HCV and Malaria Have So Far Failed - Challenges to Developing Vaccines against Immunoregulating Pathogens Shuo Li,Magdalena Plebanski,Peter Smooker,Eric J. Gowans,2016-09-14 Despite continuous progress in the development of anti viral and anti bacterial parasite drugs the high cost of medicines and the potential for re infection especially in high risk groups suggest that protective vaccines to some of the most dangerous persistent infections are still highly desirable There are no vaccines available for HIV HCV and Malaria and all attempts to make a broadly effective vaccine have failed so far In this Research Topic we look into why vaccines have failed over the years and what we have learn from these attempts Rather than only showing positive results this issue aims to reflect on failed efforts in vaccine development Coming to understand our limitations will have theoretical and practical implications for the future development of vaccines to these major global disease burdens

Immunotherapies Towards HIV Cure Carolina Garrido,Alberto Bosque,Maria Salgado,2021-07-08

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Immunosuppression-Related Swine Diseases Gang Wang,Leyi Wang ,Taofeng Du,2024-07-25 Pigs are important agricultural animals with ancient domestication history and economic value and have become important sources of protein for humans Infectious diseases affect the health of pigs and the stability and productivity of the global swine industry The emergence and reemergence of several contagious swine diseases in recent years have posed a severe threat to pig production globally Increasing concern has been raised about the immunosuppressive effect caused by immunosuppressive swine pathogens in recent years such as porcine reproductive and respiratory syndrome virus PRRSV porcine circovirus PCV African swine fever virus ASFV classical swine fever virus CSFV pseudorabies virus PRV among others Infection with variant strains of PRRSV PRV and the low virulence strains of ASFV increase the pathogenicity of opportunistic infectious agents causing secondary disease challenges which can result in more complicated clinical symptoms and severe diseases These diseases lead to increased treatment expenses reduced swine herd growth rate and feed conversion rate However with the ongoing viral evolution and the emergence of novel variants current research into the mechanisms underlying immunosuppression remains inadequate highlighting the urgent need for further investigation *Molecular Basis of Resilience* Patrick L. Iversen,2018-09-29 This book illuminates mechanisms of resilience Threats and defense systems lead to adaptive changes in gene expression Environmental conditions may dampen adaptive responses at the level of RNA expression The first seven chapters elaborate threats to human health Human populations spontaneously invade niche boundaries exposing us to threats that drive the resilience process Emerging RNA viruses are a significant threat to human health Antiviral drugs are reviewed and how viral genomes respond to the environment driving genome sequence plasticity Limitations in predicting the human outcome are described in nonlinear anomalies An example includes medical countermeasures for Ebola and Marburg viruses under the Animal Rule Bacterial infections and a review of antibacterial drugs and bacterial resilience mediated by horizontal gene transfer follow Chapter 6 shifts focus to cancer and discovery of novel therapeutics for leukemia The spontaneous resolution of AML in children with Down syndrome highlights human resilience Chapter 7 explores chemicals in the environment Examples of chemical carcinogenesis illustrate how chemicals disrupt genomes Historic research ignored RNA damage from chemically induced nucleic acid damage The emergence of important forms of RNA and their possible role in resilience is proposed Chapters 8 10 discuss threat recognition and defense systems responding to improve resilience Chapter 8 describes the immune response as a threat recognition system

and response via diverse RNA expression Oligonucleotides designed to suppress specific RNA to manipulate the immune response including exon skipping strategies are described Threat recognition and response by the cytochrome P450 enzymes parallels immune responses The author proposes metabolic clearance of small molecules is a companion to the immune system Chapter 10 highlights RNA diversity expressed from a single gene Molecular Resilience lists paths to RNA transcriptome plasticity forms the molecular basis for resilience Chapter 11 is an account of ExonDys 51 an approved drug for the treatment of Duchenne muscular dystrophy Chapter 12 addresses the question what informs molecular mechanisms of resilience that drives the limits to adaptation and boundaries for molecular resilience He speculates that radical oxygen epigenetic modifications and ligands to nuclear hormone receptors play critical roles in regulating molecular resilience

Against the Grain ,1997 *The American Review of Respiratory Disease* ,1983 Includes Abstracts section previously issued separately **Addressing the Challenges of Globalization** Uma J. Lele,Christopher D. Gerrard,2004 This report completes the second phase of the independent evaluation by the Operations Evaluation Department of the World Bank s involvement in global programmes It is based on case studies of 26 Bank supported programmes that accounted for 90 per cent of the Bank s global programme expenditure in 2002 The report seeks to draw cross cutting lessons about the design implementation and evaluation of global programmes and to identify sector specific issues **Reviews in Toxicology** ,2000

Microbiological Reviews ,1980 *Novel Concepts in Using Broadly Neutralizing Antibodies for HIV-1 Treatment and Prevention* Philipp Schommers,Harry Gristick,Marit J. Van Gils,Kshitij Wagh,2022-02-09 Annual Review of Immunology William E. Paul,1995 Cited in Chen The volumes in this series contain critical articles reviewing significant developments in the discipline Among the topics in 24 review essays hepatitis B virus immunopathogenesis prevention of AIDS transmission through screening of the blood supply transcriptional regulation of complement genes superantigens of mouse mammary tumor virus and new concepts in the immunopathogenesis of HIV infection Includes a subject index and cumulative indices of authors and titles vols 1 13 Annotation copyright by Book News Inc Portland OR **Critical Reviews in Immunology** ,1999 Annual Review of Immunology ,1995 **Government Employee Relations Report** ,1991 **Nutrition Abstracts and Reviews** ,2001 Public Meeting to Consider the Approval of Air Quality Plans for Portions of the Broader Sacramento Area California. Air Resources Board,1992 **Bangladesh, Key Challenges for the Next Millennium** ,1999 With reference to economic and social conditions of Bangladesh

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