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Clinical Significance of Viral Diagnostics

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Abstract

Diagnostics in virology has become a very important tool in both diagnosis and prognosis of a disease. Rapid and accurate diagnosis of an infection should enhance patient outcome by enabling early initiation of appropriate therapy and thus implementation of relevant infection-control measures. Virological diagnostic methods may be implemented as adjuncts to the epidemiologic investigation of infectious disease outbreaks.Thus, paving a way for the development of newer antiviral drugs. Molecular diagnostics has helped in overcoming the various challenges and has helped the clinicians in determining the appropriate therapy to be initiated.

Introduction

In medicine,clinical significance is the practical importance of a treatment effect, whether it has a real genuine, palpable, noticeable effect on daily life. A number of sensitive and

specific diagnostic tests have led to a deeper understanding of the natural history of the disease. Before antiviral therapy became available, viral diagnosis was used primarily on an epidemiological basis. In the present scenario, the discovery of a variety of antiviral drugs has in a way led to the establishment of more accurate facilities for viral diagnosis and more rapid diagnostic techniques.

Rationale for development of antiviral drugs

A severe disease with a long duration and high incidence is the ideal target for drug development. The presence of an effective vaccine is an important independent factor when the need for drug development is considered. The high cost of developing drugs has limited the number of viral diseases of public health concern to a relatively short list. The antiviral drugs which are in use and many which are being developed are highly specific for one single infectious agent. Thus, this mandates the need for accurate diagnosis of an infection before therapy.

Challenges in the development of antiviral drugs

Designing safe and effective antiviral drugs is a challenge in itself. A very important reason is that viruses replicate inside the host cells, using the cells own metabolic functions. This makes it an extremely difficult task to find targets for the drug that would interfere with the virus only. Thus, a major disadvantage is toxicity to human cells.Moreover, an important hindrance in development of new antiviral drugs is viral variation and a number of upcoming strain variants. Thenumber of viruses that have newly emerged in the last 30 years is more than 30,and have been responsible for a number of outbreaks. One prominent example is the Ebola virus outbreak in West Africa, in which it has been found that many new clades are circulating. Thus, making it extremely difficult for the development of effective antiviral drugs.

Overcoming challenges

Microbiology has now gone deep down to the level of genetic and molecular function of organisms. It has helped the researchers to comprehend the structure and function of viruses. This has paved a way for the emergence of new antiviral drugs.

Evolution of anti viral drugs

It is now 40 years since the New York Academy of Science sponsored the 1st Conference on Antiviral Substances. At that time, viral replication was thought to be carried out by cellular enzymes and the chances of selective inhibition of viral replication looked very bleak. In 1967, Kates and McAuslan described the first viral enzyme, pox virus DNA-dependent RNA polymerase. This was the first basis for selectiveantiviral drugs, which was soon to be followed by many other viral enzymes. At the 2nd Conference on AntiviralSubstances in 1969, there was quite a lot of progress in this area. Firstly, iododeoxyuridine, described earlier by Prusoffhad been shown to be active against herpes simplex. Secondly, amantadinehad been shown not only to inhibit influenza virus. Finally, interferon (IFN) and its inducers were discussed as potential and one of the most promising antiviral drugs against several different viral infections.[1]

Antiviral drugs in current clinical scenario

In the present scenario, the current armamentarium for the chemotherapy of viral infections consists of 37 licensed antiviral drugs. For the treatment of human immunodeficiency virus (HIV) infections, 19 compounds have been formally approved: (i) the nucleoside reverse transcriptase inhibitors (NRTIs) zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir and emtricitabine; (ii) the nucleotide reverse transcriptase inhibitor (NtRTI) tenofovirdisoproxilfumarate; (iii) the non-nucleoside reverse transcriptase inhibitors (NNRTIs) nevirapine, delavirdine and efavirenz; (iv) the protease inhibitors saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, lopinavir (combined with ritonavir at a 4/1 ratio) and atazanavir; and the viral entry inhibitor enfuvirtide. For the treatment of chronic hepatitis B virus (HBV) infections, lamivudine as well as adefovirdipivoxil have been approved. Among the anti-herpesvirus agents, acyclovir, valaciclovir, penciclovir (when applied topically), famciclovir, idoxuridine and trifluridine (both applied topically) as well as brivudin are used in the treatment of herpes simplex virus (HSV) and/or varicella-zoster virus (VZV) infections; and ganciclovir, valganciclovir, foscarnet, cidofovir and fomivirsen (the latter upon intravitreal injection) have proven useful in the treatment of cytomegalovirus (CMV) infections in immunosuppressed patients (i.e. AIDS patients with CMV retinitis).Following amantadine and rimantadine, the neuraminidase inhibitors zanamivir and

oseltamivir have recently become available for the therapy (and prophylaxis) of influenza virus infections. Ribavirin has been used (topically, as aerosol) in the treatment of respiratory syncytial virus (RSV) infections, and the combination of ribavirin with (pegylated) interferon-alpha has received increased acceptance for the treatment of hepatitis C virus (HCV) infections.[2] Thus, the availability of antiviral therapeutic agents that are effective for specific viral infections has created an obvious need for specific viral diagnosis.

Emerging anti viral drugs

Foremost among the newly described antiviral agents that may be developed into drugs are, for the treatment of human papilloma virus (HPV) infections, cPrPMEDAP; for the treatment of herpes simplex virus (HSV) infections, BAY 57-1293; for the treatment of varicella-zoster virus (VZV) infections, FV-100 (prodrug of Cf 1743); for the treatment of cytomegalovirus (CMV) infections, maribavir; for the treatment of poxvirus infections, ST-246; for the treatment of hepatitis B virus (HBV) infections, tenofovirdisoproxilfumarate (TDF) (which in the meantime has already been approved in the EU); for the treatment of various DNA virus infections, the hexadecyloxypropyl (HDP) and octadecyloxyethyl (ODE) prodrugs of cidofovir; for the treatment of orthomyxovirus infections (i.e., influenza), peramivir; for the treatment of hepacivirus infections (i.e., hepatitis C), the protease inhibitors telaprevir and boceprevir, the nucleoside RNA replicase inhibitors (NRRIs) PSI-6130 and R1479, and various non-nucleoside RNA replicase inhibitors (NNRRIs); for the treatment of human immunodeficiency virus (HIV) infections, integrase inhibitors (INIs) such as elvitegravir, nucleoside reverse transcriptase inhibitors (NRTIs) such as apricitabine, non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as rilpivirine and dapivirine; and for the treatment of both HCV and HIV infections, cyclosporin A derivatives such as the non-immunosuppressive Debio-025.[3]

Rationale for specific viral diagnosis

Diagnostic virology has now entered the mainstream of medical practice. Multiple methods are used for the laboratory diagnosis of viral infections, including viral culture, antigen detection, nucleic acid detection, and serology. Newer immunologic and molecular tests are

now being developed that provide more rapid results and are able to detect a larger number of viruses.Thus replacing viral culture as the mode of diagnosis. Molecular virology has significantly improved diagnosis in clinical virology. Virus discovery and rapid implementation of molecular diagnostic tests for newly discovered viruses has strongly beneficiated from the development of molecular techniques. Viral load and antiviral resistance or sub typing assays are now used as a routine practice as a part of the biological monitoring of patients chronically infected by HIV, HBV and HCV in laboratories equipped with molecular techniques.[1]

Importance of diagnosis in viral infections of public health importance

Chronic viral hepatitis and the complications associated with progressive liver disease are a global health problem. Different characteristics of viruses can affect the transmission of disease, viral pathogenesis, response to therapy and the outcome of infection. Molecular characterization of viruses has moved from the research bench to reference laboratories and clinics.Clinicians routinely examine molecular information about viruses, in regard to the various genotypes, to administer effective therapeutic interventions and make critical decisions with regards to the management of infected patients and hence the prognosis.When we talk about chronic HBV infection,the diagnostic tests currently available establish the HBV disease stage, as well as monitor the course of the disease and also the treatment response to antiviral drugs. With the use of the newer molecular diagnostic techniques it is possible to detect new infections and especially monitor HBV-infected individuals on antiviral therapy. A number of well-characterized HBV mutations have been recognized, leading to vaccine failure, loss of HBV detection by diagnostic assays, increased viral replication leading to hepatic damage, and resistance to antiviral agents.[1]Thus the significance of these variants and the problems faced in treatment require the continued evaluation of diagnostic assays and therapeutic agents. In case of chronic hepatitis C, determination of viral genotype has been identified as an important parameter that provides direction in the clinicalmanagement of patients with chronic HCV infections.[3]A clear understanding of regional genotypes is important for treatment and prognosis. It is known that HCV genotype 1 is most difficult to treat as compared to other genotypes. Currently, determination of HCV genotype has direct clinical implications for duration and dosage of

combination therapy including PEG-IFN-α with ribavirin.[3]

Hundreds of viruses cause central nervous system (CNS) disease, including meningoencephalitis and postinfectious encephalomyelitis. Routine CSF studies only rarely lead to identification of a specific etiologic agent. Diagnosis of viral infections of the CNS has been revolutionized by the advent of new molecular diagnostic technologies to amplify viral nucleic acid from CSF, including PCR, nucleic acid sequence-based amplification, and branched-DNA assay.[4]From a practical point of view, a clinician confronted with a patient with fever, headache, and altered mental status must initially distinguish encephalitis from noninfectious causes of brain dysfunction (encephalopathy). Having made this distinction, it is next necessary to distinguish cases in which brain injury is a direct consequence of viral infection from cases in which it occurs as a consequence of a postinfectious immune-mediated process (e.g., acute disseminated encephalomyelitis). Finally, the goal in cases of encephalitis is to identify a specific etiologic agent, with particular emphasis on diseases that require acute treatment, such as herpes simplex encephalitis (HSE).[5]

Need in special situations, immunocompromised population

Qualitative assays for the detection of blood borne viruses have increased safety of blood transfusion and organ transplantation. In case of CMV, antigenemia testing has value in prediction or early diagnosis of CMV-GI disease, and that real-time PCR has a more diagnostic significance. Continued induction dosing or re-induction may protect against early breakthrough CMV disease and CMV-related death among patients with rising antigenemia on preemptive therapy.[6]

Emerging viral infections

Citing another example, the influenza pandemic caused by the new H1N1 virus has by now affected all parts of India. Antiviral drugs are now available, and the most preferred one is oseltamivir, with zanamivir being an alternative.[7]Thus, diagnosis does help in the early initiation of treatment.

Conclusion

Hence, rapid and accurate diagnosis of an infection should enhance patient outcome by enabling early initiation of appropriate therapy and thus implementation of relevant infection-control measures.The development of molecular diagnostic assays, real-time PCR has brought true quantitation of target nucleic acids out of the pure research laboratory and into the diagnostic laboratory.[8]It will thus become a useful tool for screening of asymptomatic patients for infection, where there is possibility of a lack of follow-up. Rapid virological diagnostic methods may be implemented as adjuncts to the epidemiologic investigation of infectious disease outbreaks.[9,10] It is thus hoped, that the impact of the virology laboratory on the management of patients as presented here will stimulate an increased and more intelligent use of virology laboratories, improved communication and cooperation between laboratory and physician, and an increased demand for the establishment of these laboratories at institutions where none are currently available.

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