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Successes and challenges in the antiviral field

Editorial overview

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The burden of viral infections

Viral infections are the source of significant morbidity and mortality world-wide. Influenza, human immunodeficiency virus (HIV) and hepatitis virus infections alone are estimated to cause more than 2 million deaths per year. As viruses are ubiquitous, highly abundant, highly diverse in genomic structure, infect all types of cellular living organism and can adapt to replicate in different species, disease and mortality associated with viral infection will remain a significant global health concern for many years to come. New viruses with an ability to spread within the human population will continue to emerge. To a large extent, the global disease impact of such new introductions into the human population will depend on the relative pathogenicity and transmissibility of these viruses. HIV is an example of a highly effective new virus introduction into the human population, which is estimated to have occurred in the late 19th or early 20th century. HIV continues to have a significant yearly impact on human mortality, with the possibility of new multidrug resistant variants emerging in the future. Another recent new virus introduction was that of the swine origin influenza H1N1(2009) virus, which managed to spread world-wide within one year of its emergence in the human population, affecting more than 10% of the human population in a single year. While we were very lucky that the intrinsic pathogenicity of this particular virus was low, other viruses with greater propensity to cause disease may emerge in the future, as indicated by the ability of viruses from several different virus families to cause severe morbidity and mortality in humans. Intrinsic deficiencies in transmissibility tend to restrict these outbreaks, but better knowledge of the molecular features that determine pathogenicity and transmissibility, as well as treatment and prophylaxis options will help to limit the global health impact of viral infections in the future.

Why do we need antiviral drugs?

For some viruses we have successful vaccines that have significantly reduced the burden of disease, but while vaccines are an excellent prophylactic measure, they do little for those already infected. Antiviral drugs can be used therapeutically (as well as prophylactically) and can successfully treat, control, prevent and even cure infections, depending on the virus. They are particularly important for viral diseases for which vaccines do not exist and for those segments of the population in whom vaccination may not afford protection, for example, the very young, the elderly or immunologically suppressed individuals who fail to generate a protective immune response to the vaccine. Additionally, antivirals may be required in times when new viruses emerge and there is a poor antigenic fit with a vaccine, such as in years in which the influenza vaccine is mismatched with new virus variants. A successful antiviral drug must inhibit virus growth and reduce the

impact of viral disease, with a drug safety profile that provides a significant benefit-to-risk ratio for the population that needs treatment or prophylaxis.

What progress have we made and what challenges remain?

The development of HAART (highly active antiretroviral therapy) for treatment of HIV infection is probably the biggest success story in the field to date. Starting with the discovery of AZT (which received FDA approval a mere four years after the identification of HIV as the cause of AIDS) there are now approximately 25 individual drugs approved for the treatment of HIV/AIDS. These can be broken down into multiple classes including nucleoside reverse transcription inhibitors, non-nucleoside reverse transcription inhibitors, protease inhibitors, integrase inhibitors and entry or fusion inhibitors. The overriding success of HAART is the ability to suppress viral replication, prevent the progression to AIDS and prolong survival. This success became possible with the use of drug combinations that delay the development of drug resistance. While most forms of monotherapy fail rapidly, the use of the most potent combination therapies can delay treatment failure for a very long time, if the drugs are taken daily with high adherence and if there are no adverse events that require treatment change or interruption. The availability of multiple drug options in each class allows for patient individualized adjustments to be made to the combination in consideration of a patient's tolerability of certain compounds, the patient's individual pharmacology profile (e.g. differences in metabolism) and the nature of the virus (e.g. presence of pre-existing drug resistance mutations). Therefore, more patients will find an efficacious combination therapy that they can tolerate, and with good adherence to therapy it is now possible for HIV-infected individuals to have dramatically increased life expectancy, almost approaching that of uninfected persons, which is an incredible achievement. It must be noted though that the current combination therapies are not curative and safety risks associated with life-long use of antiretrovirals, and long-term chronic inflammation remaining in many patients despite successful suppression of virus replication, present medical challenges that drive the development of progressive and accelerated age-related diseases in HIV patients. In addition, new drug classes are expected to be required in the future as multidrug resistant variants that can overcome the suppressive effect of combination therapies begin to emerge.

- Siliciano and Siliciano (Recent Trends in HIV-1 Drug Resistance) provide an overview of the latest data showing declining rates of antiretroviral drug resistance and an explanation for why treatment failure is sometimes seen in the absence of resistance.

While we have an effective vaccine for hepatitis B virus (HBV), there are still an estimated 240 million people worldwide who are chronically infected with HBV and a small proportion of people who do not respond to the vaccine (5–15%). Therapeutic options for chronic HBV infections have benefited tremendously from knowledge gained during antiretroviral drug development, as like HIV, HBV encodes an essential reverse transcriptase enzyme. Therefore, the most widely used drugs for the treatment of HBV infection are nucleoside analogs, and many of these originated from HIV screens. These drugs can successfully control virus replication and prevent liver disease but patients must take them for life. As a consequence of the requirement for life-long treatment and the fact that there is only one class of antiviral agent available at this time, resistance and cross-resistance within this drug class is a problem that requires careful monitoring. We are lucky that treatment failure due to resistance development occurs much more slowly with HBV as compared with HIV, but it remains a significant issue, and additional classes of antiviral agents are needed to manage patients experiencing treatment failure, some of whom develop life threatening liver disease upon reactivation of virus replication. Also, while the overlapping reading frames within the HBV genome likely contribute to the higher barrier to resistance, this also means that drug resistance mutations in the HBV reverse transcriptase can result in mutations in the overlapping reading frame of the surface antigen which can lead to emergence of viruses with changed antigenic profiles that evade neutralization and are termed vaccine escape mutants.

- Devi and Locarnini (Hepatitis B Antivirals and Resistance) describe the different pathways to resistance development against nucleoside analogs targeting HBV, the relationship to nucleoside potency and genetic barrier to resistance and impact on HBs antigen changes.

Another significant triumph of antiviral research on the horizon is the achievement of effective antiviral therapy for hepatitis C, resulting in a sustained virologic response (which correlates strongly with the clearance of viral infection) and effectively a cure. In contrast to hepatitis B, attempts to develop an effective vaccine for HCV have not been successful to date, which may be related to the higher genetic variability of this virus. HCV causes an insidious infection resulting in a slow progression to cirrhosis and hepatocellular carcinoma in many patients. The true incidence of HCV infection is hard to gauge as acute infection is generally asymptomatic, but it is estimated that there are approximately 170 million people worldwide living with chronic hepatitis C. Before 2011 the recommended therapy was a combination of