ARHAI: antiviral resistance

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Development of antiviral resistance is a particular concern for the Advisory Committee on Antimicrobial Resistance and Healthcare-Associated Infections (ARHAI). Over the last 4 years, considerable time has been devoted to examining the ability of the UK to monitor the presence and transmission of antiviral resistance. Resistances to antiviral agents in influenza virus, HIV and hepatitis B and C viruses were identified as the main targets. The emphasis is on a network of laboratories that are able to perform diagnostic tests for resistance and to participate in surveillance programmes with co-ordination either through a central reference facility in the HPA or a collaborative study group.

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Introduction

Over the past decade there has been a significant increase in both the number and the repertoire of licensed chemotherapeutic agents against viral infections. There are at present >40 licensed antiviral agents available for use, targeting a wide range of viruses, including herpesviruses, HIV, hepatitis B virus (HBV), hepatitis C virus (HCV) and influenza viruses. Many new agents are in various phases of clinical trials, and no doubt even more antiviral agents will be available for use in the next decade.

Owing to the infidelity of the viral nucleic acid replication system in many viruses, mutations occur during viral replication. In some virus infections, such as those caused by HIV and HCV, the virus in an individual patient exists as a swarm of related viruses known as a quasi-species. The use of antiviral agents drives selection pressure and preferentially selects mutations conferring antiviral resistance. This is of great concern to the Advisory Committee on Antimicrobial Resistance and Healthcare-Associated Infections (ARHAI). It is important that the UK has a surveillance system to monitor the prevalence of resistance, to evaluate its impact and to have a programme to ensure that antiviral agents are used wisely and to their greatest potential. Antiviral resistance in influenza, HIV, HBV and HCV were targeted by ARHAI for evaluation and discussion. Figure 1 summarizes the issues associated with each virus and the recommendations from ARHAI.

Influenza

Oseltamivir and zanamivir are neuraminidase inhibitors that block the release of influenza A and B viruses from infected cells, thus preventing the virus from completing its life cycle.1 Both drugs are licensed for the prevention as well as treatment of influenza virus infection. To be effective, the treatment has to be started early during the clinical course and ideally within 48 h of the onset of symptoms. Being an oral formulation, oseltamivir is a more popular drug choice than zanamivir, which is administered by inhalation.

Mutations in the neuraminidase protein can result in drug resistance. Resistance mutations have been found in seasonal influenza A/H1N1, A/H3N2 and B viruses, as well as the avian influenza A/H5N1 and more recently the pandemic 2009 A/H1N1 virus.2–4 During the 2007–2008 pre-pandemic influenza season, a significant proportion of the circulating H1N1 viruses in Europe had a mutation that changed the histidine residue in position 275 to tyrosine (H275Y),5 resulting in a conformational change in the active binding site for oseltamivir and rendering the virus resistant to the drug. However, this change has no effect on zanamivir, to which the seasonal H1N1 virus remained susceptible. Other recognized single amino acid changes in or around the active site that reduce virus susceptibility to oseltamivir include R292K, N294S or E119V in N2, and R152K or D198N in B neuraminidase. The R292K mutation also confers cross-resistance to zanamivir.6 Other rarer mutations that selectively reduce zanamivir susceptibility have also been described.7,8

The neuraminidase of the pandemic 2009 H1N1 virus only infrequently shares the H275Y mutation that was widespread among its seasonal H1N1 predecessor. Since the UK government recommended and stockpiled oseltamivir for the pandemic, it was a relief that the selected chemotherapeutic agent was effective against the pandemic strain. However, there is no room for complacency, as resistance could develop rapidly. An outbreak of transmission of oseltamivir-resistant 2009 H1N1 virus was reported among a group of immunosuppressed patients in a
The recognition of the ease of development of resistance in immunocompromised patients led to the development of revised management guidelines by the HPA during the third wave of the pandemic in the winter of 2010–2011. Zanamivir, rather than oseltamivir, was preferred as the first-line therapy in severely immunocompromised patients. ARHAI has recommended that the HPA incorporate monitoring of resistance into the existing influenza surveillance system at the local laboratory level and that the capacity should be made available across the UK. A self-swabbing scheme was successfully implemented to obtain information from the community. A network of local HPA laboratories have since adopted a real-time PCR method to detect the single-nucleotide polymorphism of H275Y mutation. This test is backed up and confirmed by the National Influenza Centre at HPA Colindale with techniques including phenotyping and pyrosequencing.

One of the major challenges ahead is the ability of the system to respond to the uncertain nature of influenza epidemics. Experience from the 2009–2010 pandemic showed that it could be difficult to formulate policy during an active epidemic when information changes from day to day. It was also shown that co-operation between the public health and professional bodies and good regular communication during the pandemic is the key to satisfactory national outbreak management. This will need to be replicated and enhanced for successful intervention of future influenza epidemics and pandemics.

**HBV**

There have been recent significant advances in the management of chronic hepatitis B, with several newly licensed nucleoside/nucleotide analogues available. Up-to-date guidelines for the management of hepatitis B are available from the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver.

Lamivudine used to be a popular first-generation nucleoside analogue with potent activity against the reverse transcriptase of HIV and HBV. Unfortunately lamivudine has a very low genetic barrier to resistance. The occurrence of the mutation M204V/I, which confers high-level resistance to lamivudine, is
common in HBV and can be detected in 14–32% of patients after 1 year of treatment and up to 60–70% after 5 years of treatment. Adefovir can be used in conjunction with lamivudine in the presence of M204V/I, but resistance to adefovir has also been reported to occur in up to 20% of patients after 2 years. Another newer nucleoside analogue, telbivudine, is also prone to the development of the resistance-associated mutation M204V/I and is not recommended by the National Institute for Health and Clinical Excellence (NICE). Currently the use of lamivudine and adefovir has been largely superseded in western countries with the arrival of second-generation anti-HBV agents such as tenofovir and entecavir. So far, very little resistance has been reported against tenofovir. However, entecavir is partially susceptible to the resistance-associated mutation selected by lamivudine. Nevertheless, development of full resistance to entecavir requires a two-hit mechanism with initial selection of M204V/I followed by several entecavir-specific mutations. As a result, treatment failure due to entecavir resistance is rare and is observed only in 3.6% of patients after 96 weeks of treatment.

Baseline resistance in HBV has not been an issue in the past. Owing to the widespread and continual use of lamivudine in some countries, and the context of the use of lamivudine as part of the therapy for HIV, baseline resistance in HBV could become an increasing problem, and this may compromise the use of second-generation agents such as entecavir. ARHAI is constantly reviewing this situation. Laboratories that perform HBV resistance genotyping are encouraged to submit their sequences to the HPA-hosted HepSEQ repository database for HBV strains (http://www.hpa-bioinformatics.org.uk/HepSEQ-Research/).

HIV

Currently there are two parallel epidemics in the UK. The epidemic in men who have sex with men (MSM) is mainly caused by subtype B virus. In contrast, the epidemic in heterosexuals is largely focused on people of sub-Saharan origins and is caused by multiple non-B subtypes, although there is now evidence for cross-over of viruses between these two groups, and the numbers of new diagnoses are increasing in both groups. Currently six classes of drugs are available for the treatment of HIV. Hence additional treatment options are available for patients with triple-class drug failure. A network of clinical virology laboratories currently provides a genotypic HIV resistance service in the UK. Co-ordinating activities within this network are led by the HPA and include regular meetings, training activities and the provision of quality controls, and there is the potential to extend this activity to HCV (see below). As drugs directed at new targets, such as integrase, have become available, the new assays required to analyse resistance to these drugs have been rolled out through the laboratory network. The resistance data generated from this network are submitted to a central database held at the MRC Clinical Trials Unit and overseen by the UK Collaborative Group on HIV drug resistance (http://www.ctu.mrc.ac.uk/hivrdb/). Many HIV units are part of the collaborative centres of the UK Collaborative HIV Cohort (UK CHIC) study (http://www.ukchic.org.uk), which captures clinical patient data, and such information can be linked to the HIV drug resistance database. This serves as a unique and invaluable source of information and should continue to be funded. National surveillance of HIV drug resistance is a major research activity of the collaboration. Annual reports from the HIV drug resistance database include analyses of current levels of resistance in patients failing therapy and also levels of transmitted resistance, i.e. drug resistance in newly diagnosed treatment-naive patients.

Among drug-experienced patients who have experienced virological failure, the prevalence of resistance fell markedly from a peak of 78% in 1999 to 44% in 2007. This is due in part to an increasingly lower clinical threshold for resistance testing, but also possibly due to the increased use of ritonavir-boosted protease inhibitors, which has been observed, patients may fail without detectable resistance mutations.

Transmission of drug-resistant HIV strains from person to person peaked in 2002, with about 14% of new diagnoses tested showing primary resistance, however, this then fell to about 8% by 2008, possibly due to improved treatment; however, the levels of transmitted resistance are now possibly increasing again. Transmitted resistance is usually stable in the recipient patient and now there is evidence for sustained onward transmission of drug-resistant lineages. Clearly it is essential to maintain this surveillance in order to guide appropriate public health interventions.

HCV

There has been a steady increase in the number of deaths caused by HCV-related end-stage liver disease and hepatocellular carcinoma. There is on-going transmission of HCV in the community, particularly among intravenous drug users. In 2008, >10000 new cases of hepatitis C were diagnosed in the UK. Despite this, the actual pool of infected individuals is expected to be much higher, as it was estimated that as many as 80% of individuals with hepatitis C infection are unaware of their diagnosis. ARHAI agreed that a national registry for HCV should be established to build up the basic epidemiological database. To ensure the quality of the data collection at the regional/local level, the development of a national dataset should be a priority. In order to look at outcomes, longitudinal data are required. Although progress has been made, such a database is still not available.

Pegylated interferon and ribavirin is currently the standard of care for the treatment of chronic hepatitis C. While this is highly successful for genotype 2 or 3 HCV infection, up to 50% of patients infected with HCV genotype 1 or 4 failed to achieve a sustained virological response (SVR). More recently, a host genetic polymorphism in the IL28b gene was found to have significant correlation to treatment response in patients infected with HCV genotype 1. Direct-acting antiviral agents are being developed to supplement or replace the current treatment approach. Drugs under development include protease inhibitors and polymerase inhibitors. The development of protease inhibitors is further ahead, with telaprevir and boceprevir leading the field. Both have been shown to be more effective in combination with standard therapy at achieving SVR than standard therapy alone. Due to the low genetic barrier to resistance, there are major concerns that high-level resistance to these agents will develop quickly.
There are currently no data available on the level of resistance that occurs when used in combination with standard therapy and whether the resistant mutation is archived after the agent is stopped. In addition, natural resistance occurs in some strains of HCV.

ARHAI recognizes that it is important for resources to be in place to allow virological testing to identify resistant strains. The network of clinical virology laboratories that currently provides HIV genotypic resistance testing could also provide the capacity to carry out HCV genotyping. The results of a survey of virology laboratories in the UK with the potential to carry out molecular genotyping demonstrate that having the appropriate methods and funding for testing are the key issues. Commissioning is considered the appropriate approach, as with HIV, and this should progress before new drugs become available. Concerns were also raised about the possibility of transmission of resistant strains of HCV among intravenous drug users. The need to maintain links with NICE over guidance development was stressed. ARHAI is also working closely with the Department of Health Advisory Group on Hepatitis (AGH) to monitor the situation.

Conclusions

The successful control of antiviral resistance and the transmission of resistant viruses is dependent on the ability to detect antiviral resistances in the clinical setting and in population surveillance. ARHAI strongly recommends continuation of the current effort to collect and monitor such information.

Transparency declarations

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