Neuraminidase inhibitors (NAIs) are antiviral drugs for treatment and prophylaxis of influenza. By blocking the activity of the enzyme neuraminidase, NAIs prevent new viral particles from being released. The increasing use of NAIs brings into focus the risk of drug resistance arising to the class. There are three levels of antiviral resistance according to the way that resistance can be detected or inferred: genotypic, phenotypic and clinical resistance. For many years seasonal influenza viruses resistance to NAIs was low (0.33%). Recently, there has been described an increasing number of resistant seasonal influenza strains to oseltamivir (2% in adults, 5–18% in children). In 2007 there were published data describing 14% resistant to oseltamivir strains of influenza A/H1N1/ in Europe. Approximately 0.5–1.0% of influenza A/H1N1/ pdm09 isolates are currently resistant to oseltamivir. The established markers of the resistance to oseltamivir were found in 2.4% of human and 0.8% of avian isolates of influenza A/H5N1/. It has been not observed a cross resistance among oseltamivir and zanamivir. NAIs resistance in influenza viruses is relative and despite its presence patients with resistant viruses may still benefit from receiving these antivirals. The response to treatment with antivirals remains the most important proof of antiviral effectiveness. The rational use of NAIs is essential to preserve the best choice for treatment and prophylaxis of seasonal, avian and pandemic influenza.

RESISTANCE TO NAIS — GENERAL CONSIDERATIONS

The problem of resistance of influenza viruses to NAIs is of the high importance and that’s why there has been created the global Neuraminidase Inhibitor Susceptibility Network (NISN) which coordinates the analysis of clinical isolates collected thought the World Health Organization (WHO) surveillance network. Surveillance of the antiviral susceptibility of influenza viruses circulating in Europe has been established in 2004 though the European Union-funded European Surveillance Network for Vigilance against Viral Resistance (VIRGIL), in collaboration with European Influenza Surveillance Scheme (EISS), WHO and national influenza centers (Monto et al., 2006).

There are generally three levels of antiviral resistance according to the way that resistance can be detected or inferred (EMA, 2013):

- genotypic resistance (detecting though sequencing of the viral genome and identification of mutations previously associated with certain level of drug resistance);
- phenotypic resistance (resistance of the virus to drugs is tested in vitro by measuring viral replication at a different drug concentrations);

Key words: influenza, resistance, neuraminidase inhibitors

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SARS-CoV-2 infections of lungs, liver, kidneys, and central nervous system. The presence of viral RNA in the reservoirs can be detected using polymerase chain reaction (PCR) assays. Therefore, it is crucial to develop effective antiviral strategies to combat the COVID-19 pandemic.

In conclusion, the comprehensive understanding of SARS-CoV-2 biology and pathology is critical for the development of effective antiviral therapies. The continuous monitoring of the mutation patterns and the emergence of drug-resistant variants are essential to ensure the effectiveness of existing antiviral drugs. Moreover, the development of new antiviral classes and combination therapy approaches may offer potential solutions to combat the COVID-19 pandemic.

References:

Figures:
- Figure A: SARS-CoV-2 genomic organization and genome structure.
- Figure B: The interaction of SARS-CoV-2 Spike protein with ACE2 receptor.
- Figure C: The viral life cycle of SARS-CoV-2 in the host cell.

Tables:
<table>
<thead>
<tr>
<th>Parameter</th>
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Table 1: Summary of SARS-CoV-2 Genome Features.
AVIAN INFLUENZA VIRUSES RESISTANCE TO NAIS

According to the WHO classification there are highly pathogenic avian influenza viruses (HPAI), including influenza A/H5N1, A/H7N7, A/H7N9, A/H10N8 and low pathogenic avian influenza viruses (LPAI), including influenza A/H9N2/ virus (WHO, 2014).

Oseltamivir is a drug of choice for the treatment of patients infected with influenza A/H5N1/ virus. Two different strains of highly pathogenic avian influenza A/H5N1/ have been circulating since 2003: clade 1 has been found in Vietnam, Thailand, Cambodia, Lao People's Democratic Republic and Malaysia; clade 2 emerged and spread from People's Republic of China to Indonesia, Europe and Africa in 2004–2005 (WHO, 2007, Yuen & Wong, 2005). It has been shown that compared to clade 1 isolates from 2004, some clade 1 Cambodian isolates and clade 2 Indonesian isolates from 2005 demonstrate a reduced sensitivity to oseltamivir (by phenotyping testing). The decrease in sensitivity may be due to drift mutations rather than from an exposure to oseltamivir (Yen et al., 2001; Tran et al., 2004; Chotpitayasununondth et al., 2005). Some other reports describing the emergence of the resistance in influenza A/H5N1/ viruses isolated from patients in Vietnam and Egypt were published. Patients were treated with oseltamivir, and the resistant strains carried mutations causing substitutions H274Y or Asn294Ser (de Jong et al., 2005; Le et al., 2005; WHO, 2014). Up till now, the established markers of the resistance to oseltamivir were found in 2.4% of human and 0.8% of avian isolates of influenza A (H5N1) (Govorkova et al., 2013). Regarding other than influenza A (H5N1) viruses, some data indicate that an influenza A/H7N9/ isolate, encoding the R292K substitution, is highly resistant to oseltamivir and peramivir, and partially resistant to zanamivir (Sleeman et al., 2013).

CONCLUSIONS

The resistance to NAIs among influenza viruses is an emerging problem of the high epidemiological and clinical impact. The rational use of NAIs is essential to preserve the best choice for treatment and prophylaxis of seasonal, avian and pandemic influenza.

REFERENCES


