

**KSZTAŁCENIE USTAWICZNE •
CONTINUOUS MEDICAL EDUCATION (CME)****Neuraminidase inhibitors resistance in influenza viruses
– a current medical problem****Oporność na inhibitory neuraminidazy – współczesny problem medyczny**ANETA NITSCH-OSUCH^{1, A, B, D-F}, LIDIA BERNADETA BRYDAK^{1, 2, A, B, D-F}¹ Department of Family Medicine, Warsaw Medical University

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Streszczenie Inhibitory neuraminidazy, takie jak oseltamiwir i zanamiwir, są ważną grupą leków przeciwwirusowych, stosowanych w profilaktyce i leczeniu grypy: sezonowej, ptasiej i pandemicznej. Coraz częstsze stosowanie inhibitorów neuraminidazy może sprzyjać pojawieniu się i nasileniu zjawiska lekooporności wirusów grypy na tę grupę leków – podobnie jak wystąpiło to w przypadku adamantanów. Wyróżnia się trzy rodzaje oporności na leki przeciwwirusowe: genotypową, fenotypową i kliniczną. Przez wiele lat oporność na inhibitory neuraminidazy pozostawała na bardzo niskim poziomie (0,33% szczepów). W ostatnich latach obserwowane jest zwiększanie liczby szczepów wirusów grypy opornych na oseltamiwir (2% u dorosłych, 5–6% u dzieci). W 2007 r. opublikowano dane europejskie wskazujące na 14% szczepów H1N1 opornych na oseltamiwir. Jak dotąd nie stwierdzono oporności krzyżowej między oseltamiwirem i zanamiwirem – co może wynikać z różnicy podanych dawek leków, różnic w budowie i właściwościach farmakokinetycznych leków. Należy podkreślić, że laboratoryjne stwierdzenie oporności nie wyklucza klinicznej skuteczności leków przeciwwirusowych. W celu uniknięcia narastania oporności na leki przeciwwirusowe ich stosowanie powinno być bardzo racjonalne, tzn. użycie powinno być poprzedzone potwierdzeniem rozpoznania grypy w badaniach laboratoryjnych. Konieczna jest międzynarodowa i stała współpraca w celu monitorowania oporności wirusów grypy na inhibitory neuraminidazy w celu zapewnienia ich skutecznego działania podczas stosowania profilaktycznego i terapeutycznego w przypadku grypy sezonowej, grypy ptasiej, jak i grypy pandemicznej.

Słowa kluczowe: inhibitory neuraminidazy, oseltamiwir, zanamiwir, oporność.

Summary Influenza virus neuraminidase inhibitors (NAIs) – oseltamivir and zanamivir – are an important class of antivirals for the treatment and prophylaxis of influenza: seasonal, avian and pandemic influenza. Increasing use of NAIs brings into focus the risk of drug resistance arising to the class. There are generally three levels of antiviral resistance: genotypic, phenotypic and clinical resistance. For many years influenza viruses' resistance to NAIs was low (0.33%). 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 strains H1N1 in Europe. It should be underlined that oseltamivir resistance in influenza viruses is relative and despite its presence patients with oseltamivir-resistant viruses may still benefit from receiving oseltamivir. Clinical resistance and the response to treatment with antivirals remains the most important proof of antiviral effectiveness. Oseltamivir is the drug of choice for treatment of avian influenza in humans (single cases of resistant strains were described). Currently it has been not observed a cross-resistance among oseltamivir and zanamivir which may be a consequence of number of given doses, differences in drug structure and duration of drug concentrations in site of infection. Global collaboration, phenotypic and genotypic testing of drug sensitivity of circulating influenza viruses for neuraminidase inhibitors sensitivity are critical in order to provide an effective prophylaxis and treatment of the diseases caused by these influenza viruses.

Key words: neuraminidase inhibitors, oseltamivir, zanamivir, resistance.

Background

Neuraminidase inhibitors (NAIs), including oseltamivir and zanamivir, are an important class

of antivirals for the treatment and prophylaxis of influenza.

In contrast to the older class of antivirals – the adamantanes (amantadine and rimantadine) –

NAIs are effective against both influenza virus type A and B, they are associated with less side effects and a better profile concerning drug-resistance [1].

A problem of drug-resistance has already been described among the adamantanes. Adamantane-resistant isolates of influenza A viruses are generally stable, can be transmitted to susceptible contacts and can be shed for prolonged periods in immunocompromised patients taking the drug. This potential for the development of resistance especially limits the use of the adamantanes for the treatment and prophylaxis of seasonal influenza – according to ACIP recommendations these drugs should not be used during epidemic influenza (90% of viruses are resistant) [2]. Adamantanes are not recommended for the treatment and prophylaxis of avian influenza [3].

Because of a high resistance of influenza virus to adamantanes, the newer group of antivirals – neuraminidase inhibitors seems to be a best choice for the treatment and prophylaxis for seasonal influenza, avian influenza and future pandemic influenza.

Rational usage of NAIs is necessary to preserve their potential power in fighting against H5N1 virus infection and future pandemic, that why the problem of influenza viruses to NAIs should be considered as current medical problem of a high impact and it is worth to present for general practitioners.

Mechanism of action of NAIs

The neuraminidase inhibitors interfere with the release of progeny influenza virus from infected host cells. All influenza viruses bear two surface glycoproteins: a hemagglutinin and a neuraminidase. The neuraminidase – the target molecule of the neuraminidase inhibitor compounds – cleaves the cellular-receptor sialic acid residues to which the newly formed particles are attached. Without neuraminidase, infection would be limited to one round of replication [2, 4].

Indications for NAIs

Seasonal influenza

Both oseltamivir and zanamivir are recommended for treatment and prophylaxis of seasonal influenza. Early initiation of treatment (max. 36–48 hours after the onset of symptoms) provides the reduction of duration of symptoms (mostly fever); treated patients have a lower frequency of secondary complications [5–7]. Several large, controlled studies have demonstrated that

both zanamivir and oseltamivir are effective (70–90%) in preventing clinical influenza in healthy adults when the drugs are used either as prophylaxis after exposure for close contacts, such a household members or as seasonal prophylaxis in the community [8–10].

Avian influenza

Oseltamivir is a drug of choice for treatment influenza caused by H5N1 virus, up to date there is lack of knowledge about patients treated with zanamivir, although it is active against H5N1 virus in an animal model and *in vitro* [11, 12].

Oseltamivir and zanamivir may be used in prophylaxis of avian influenza [11–13]. Workers should receive an influenza antiviral drug daily for the duration which direct contact with infected poultry or contaminated surfaces occurs. Chemoprophylaxis against H5N1 infection should not be routinely offered to low-risk groups, including health-care workers without a direct exposure to H5N1 infection or healthcare or poultry workers who used appropriate protective equipment during a potential exposure [13, 14].

Pandemic influenza

The potential impact of pandemic influenza makes effective measures to limit the spread and morbidity of virus infection a public health priority. Antiviral drugs are seen as essential requirements for control of initial influenza outbreaks caused by a new virus, and in pre-pandemic plans there is a heavy reliance on drugs stockpiling [15]. WHO recommends stockpiling antivirals (both oseltamivir and zanamivir) for 25% of population while American Infectious Diseases Society – for 50% [11, 15].

Resistance to NAIs

A key advantage of neuraminidase inhibitors, and a major difference from the adamantanes, is the development of resistance is very rare (< 1%) [1]. The problem of resistance is of a high importance and that is way there has been created the global neuraminidase inhibitor susceptibility network (NISN) which coordinates the analysis of clinical isolates collected through the WHO surveillance network. Surveillance of the antiviral susceptibility of influenza viruses circulating in Europe has been established in 2004 through 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 [16].

There are generally three levels of antiviral resistance according to the way that resistance can be detected or inferred [17]:

- genotypic resistance (detecting through 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* (not in living systems) by measuring viral replication at a different drug concentrations (IC_{50});
- clinical resistance (based on animals (ferret or mice) and human patients and measuring or observing the actual response to treatment with antivirals.

Resistance to neuraminidase inhibitors may be due to mutations in haemagglutinin, which often confers resistance to both zanamivir and oseltamivir, while mutation in neuraminidase may render oseltamivir ineffective but retains susceptibility to zanamivir [18].

Resistance to oseltamivir

Viral resistance to oseltamivir may develop by alteration of the amino acid composition of neuraminidase or by alteration in the affinity of haemagglutinin to the receptors on the cell surface, in addition, according to a recent study, a few influenza strains may completely lack of neuraminidase activity, which may also result in viral resistance to neuraminidase inhibitor. Resistant strains have been generated *in vitro* and such strains have also been found in a small proportion of patients during or after treatment of oseltamivir. Oseltamivir-resistant strains have also been detected in individuals not exposed to oseltamivir. Mutations in the viral neuraminidase gene can be generated *in vitro* by repeated passages in the presence of low concentrations of oseltamivir [18, 19].

So far, about 50 million of doses of oseltamivir have been given to patients all over the world, in patients treated with oseltamivir the incidence of resistant viruses was estimated for 1–2% in adults and 5–6% of children [20, 21]. The clinical course of influenza in oseltamivir treated patients, from whom the resistant viruses were isolated, appeared to be similar to that with wild-type virus [20, 21]. Predominant mutations of NA were Arg292Lys and Glu119Val in H3N2 virus. Oseltamivir resistant virus was isolated from 16.3% of Japanese children treated with oseltamivir for influenza A (H3N2) infections (2004) [22]. The small number of children in this examination (43) is also found as a limitation of its results, however it is underlined that the rate of the oseltamivir-resistance in children should be

of concern because children are the most important source of the disease and play a vigorous role in the transmission of the disease [22].

According to NISN the susceptibility of 2287 from 1999–2002 was monitored and 8 isolates (0,33%) had reduced (> 10-fold) susceptibility to oseltamivir and 6 resistance-associated mutations. None were from patients who were known to have received NAIs. Further clinical isolates with oseltamivir resistance-associated mutations were detected by NISN in Japan during the 2003–2006 influenza seasons [16]. The clinical significance of oseltamivir-resistance strains of influenza appears to be limited because of reduced infectivity, replicative ability and pathogenicity of the resistant strains [16,17].

The significance of the resistant strains observed in individuals who were not exposed to oseltamivir is unclear at the present. Such a situation was described in 2007/2008 seasons in Europe. Results from analysis of the early winter (November 2007–January 2008) A (H1N1) virus isolates has revealed a significant proportion, approximately 14% of European strains resistant to oseltamivir (Tamiflu), but retain sensitivity to zanamivir (Relenza) and the adamantanes [26]. Oseltamivir resistance viruses have been detected in 9 countries (Denmark, Finland, France, Germany, Netherlands, Norway, Portugal, Sweden and United Kingdom), in particular in Norway (70%), France (17%) Germany (7%) and Great Britain (5%) carry the same mutation causing the substitution of histidine by tyrosine at residue 274 (H274Y) of the neuraminidase, which is known to confer a high level resistance to oseltamivir. All these viruses remain sensitive to the other anti-neuraminidase drug zanamivir and to the anti M2 drugs amantadine and rimantadine. There was no information that these viruses were isolated from patients who had been either treated with oseltamivir or been in a close contact with another individual treated with this drug [23].

These finding indicates the necessity for a careful virological and epidemiological surveillance concerning oseltamivir resistance but it is also agreed that there is currently insufficient evidence for authorities to consider changes to clinical guidelines [24].

There is also currently no evidence that the mutated H1N1 viruses are more virulent than other strains of seasonal influenza (all the Norwegian patients had typical influenza illness symptoms) [17, 24].

What should be also underlined, oseltamivir resistance in influenza viruses is relative and despite its presence patients with oseltamivir-resistant viruses may still benefit from receiving oseltamivir. The clinical course for patients with

resistant viruses and treated with antivirals is not any different from patients carrying fully sensitive strains. Clinical resistance and the response to treatment with antivirals (the clinical response) remains the most important proof of antiviral effectiveness [17, 24].

Resistance to zanamivir

In vitro studies have shown that mutations in both haemagglutinin and neuraminidase are associated with resistance development over prolonged passage (but the clinical significance of HA mutations is unknown) [18].

The susceptibility of 2287 isolates from 1999–2002, post-licencesure of the neuraminidases, was monitored and only two isolates (0.1%) had reduced susceptibility to zanamivir and possible resistance-associated mutations. The clinical usage of zanamivir is still limited (according to information provided by a producer – till now 70,000 doses of a drug have been administered to patients) but, for so far, zanamivir-resistant viruses have not been isolated from immunocomponent individuals who have received zanamivir [16]. One resistant virus was isolated from an immunocompromised child after bone-marrow transplantation infected with type B influenza virus [28]. The mutant showed a small decrease in sensitivity to zanamivir in infected mice but there was no detectable resistance to zanamivir in ferrets. Immunocompromised patients have difficulties with cleaning virus and this appears to promote a selection of drug resistance virus.

As with oseltamivir, mutations that confer resistance to zanamivir may also reduce the virulence of the virus. Up to date influenza virus strains which are resistant to oseltamivir stay susceptible to zanamivir – *in vitro*. Lack of a cross-resistance between oseltamivir and zanamivir may be explained by the longer usage of oseltamivir and a limited number of zanamivir dosages, but there are other hypotheses, which are presented to describe lack of cross-resistance [25].

It is possible that differences in chemical structure and binding to the NA catalytic site result in different drug resistance profiles. This has been attributed how closely the compounds mimic the transition state analog for NA. Hence zanamivir, which closely resembles the natural substrate for NA, has a low resistance index [26].

Although both drugs, zanamivir and oseltamivir, are based on the transition state analog of sialic acid, zanamivir has a single substitution of a guanidine group at the 4'position on the sugar ring, whereas oseltamivir has an amino group at

the 4 position and, more importantly, a bulky hydrophobic pentyl ether group replacing the glycerol side chains at 6'position. Reorientation of E 276 in the active site is required to create a hydrophobic pocket necessary to accommodate thospentyl ether group. Mutations that prevent this reorientation occurring, lead to high levels of specific oseltamivir resistance (H 274Y, R292K), while for zanamivir this reorientation is not required [26–29].

It is also considered that differences in the mode of delivery and pharmacokinetics of zanamivir have implications for drug resistance. Differences in concentrations of NAIs at the site of viral replication could contribute to differences not only in efficacy but also to the risk of emergence of NAI resistant viral strains. Low drug concentrations, which only partly block viral replication, could enhance the risk by providing an environment for drug resistance virus to emerge [26].

Resistance of H5N1 to NAIs

Oseltamivir is a drug of choice for treatment of patients infected with H5N1 influenza virus [30]. The treatment should be implemented as early as possible (because of mentioned mechanism of action of NAIs). Up to date there has been notified 409 cases of avian influenza in humans, among them 256 (> 60%) were fatal (status for 2 March 2009) [30]. Reasons of high mortality among people infected with H5N1 virus were found: late diagnosis and late introduction of treatment with oseltamivir. Currently experts postulate higher doses (150 mg twice a day) and longer duration of treatment (7–10 days versus traditional 5 days) [31–33].

Two different strains of highly pathogenic aian 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. It has been shown that compared with clade 1 isolates from 2004, some clade 1 Cambodian isolates and clade 2 Indonesian isolates from 2005 demonstrate reduced sensitivity to oseltamivir (by phenotyping testing) [28].

It is necessary to underline that according to a recent report from Neuraminidase Inhibitor susceptibility Network, 96/97 (99%) H5N1 human and poultry isolates tested by WHO and CDC were sensitive to oseltamivir [29]. However, a few report of emergence of oseltamivir resistance in viral isolates from osletamivir-treated patients with H5N1 infection in Vietnam and Egypt have been published [34–36].

Table 1. The use of neuraminidase inhibitors in prophylaxis and treatment of seasonal influenza (after [1])

Drug	Treatment	Prophylaxis
zanamivir	10 mg (2 inhalations) 2 × a day Duration: 5 days Age limits: > 5 years Formulation: powder for inhalations by diskhaler	10 mg (2 inhalations) 1 × a day Duration: contact prophylaxis: 10 days social prophylaxis: 28 days Age limits > 5 years Formulation: powder for inhalations by diskhaler
oseltamivir	Doses depend on body mass in children: 30–75 mg/2 × a day Adults: 75 mg 2 × a day Duration: 5 days Age limits: > 1 year Formulations: Suspension Capsules 30,45 and 75 mg	Doses depend on body mass in children: 30–75 mg 1 × a day Adults: 75 mg 1 × a day Duration: Contact prophylaxis: 10 day Social prophylaxis: 6 weeks Age limits: > 1 year Formulations: Suspension Capsules 30,45 and 75 mg

In vitro studies indicate that oseltamivir is likely to be effective also against other viruses with a pandemic potential (H9N2, H7N7) the great majority of the currently circulating H5N1 [17].

Data from animal models suggest that zanamivir is effective against H5N1 virus that caused fatal illness in Hong Kong in 1997. Intranasally administered zanamivir protects mice against lethal challenge, reducing viral replication in the lungs and reducing morbidity and mortality. The H5N1 isolate from Vietnam (A/Hanoi/390408/2005) has also been shown to be sensitive to zanamivir in the ferret mode [17, 26].

Directions for general practitioners

Neuraminidase inhibitors, oseltamivir and zanamivir, are potent antivirals for prophylaxis and treatment of seasonal influenza, avian influenza and future pandemic influenza. In order to limit the risk of spreading resistant strains of influenza viruses to neuraminidase inhibitors it is necessary to carefully diagnose and treat all cases of seasonal influenza – it is also a challenge for general practitioners. Diagnostic procedures should include rapid tests and immunofluorescent tests, and they should be more often used in every day practice. Using of antivirals for seasonal influenza treatment (not longer than 5 days) and prophylaxis (10 days) should be limited only to laboratory confirmed cases. Doses of NAIs in prophylaxis and treatment of influenza presents Table 1 [1].

References

1. Brydak LB. *Grypa, pandemia grypy, mit czy realne zagrożenie*. Wyd. 1. Warszawa: Wydawnictwo Rytm; 2008: 4–34, 200–233, 270–298, 320–367.
2. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2007; 56: 1–54.

Each general practitioner should be familiar with antivirals – oseltamivir and zanamivir, including doses, side effects, indications and contraindications, because of the essential role of these medicines in fighting against seasonal and pandemic flu.

Conclusions

1. Global collaboration, phenotypic and genotypic testing of drug sensitivity of circulating influenza viruses for neuraminidase inhibitors sensitivity are critical.
2. There is a trend of increasing number of seasonal influenza viruses resistant to oseltamivir but this data should be interpreted very precisely: clinical resistance and the response to treatment with antivirals (the clinical response) remains the most important proof of antiviral effectiveness. There have been described clades of H5N1 virus resistant to oseltamivir.
3. Up to now there has not been described a cross-resistance between neuraminidase inhibitors: oseltamivir and zanamivir among seasonal and avian influenza viruses.
4. General practitioners should be familiar with actual epidemiological and virological situation concerning influenza and possess general knowledge about antivirals such as oseltamivir and zanamivir.

3. Lye D, Ang B, Leo Y. Review of human infections with avian influenza H5N1 and proposed local clinical management. *Ann Acad Med Singapore* 2007; 36: 285–292.
4. Moscona AM. Neuraminidase inhibitors for influenza. *N Engl J Med* 2005; 353: 1363–1374.
5. Monto AS, Fleming DM, Henry D. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza A and B virus infection. *J Infect Dis* 1999; 180: 254–261.
6. Treanor JJ, Hayden FG, Vrooman PS. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. *JAMA* 2000; 283: 1016–1024.
7. Nicholson KG, Aoki FY, Osterhaus AD. Efficacy and safety of oseltamivir in treatment of acute influenza a randomized controlled trial. *Lancet* 2000; 355: 1845–1850.
8. Hayden FG, Gubareva LV, Monto AS. Inhaled zanamivir for the prevention of influenza in families. *N Engl J Med* 2000; 343: 1282–1289.
9. Hayden FG, Belshe R, Villanueva C. Management of influenza in households: a prospective, randomized comparison of oseltamivir treatment with or without post-exposure prophylaxis. *J Infect Dis* 2004; 189: 440–449.
10. Wellive R, Monto AS, Carewicz O. Effectiveness of oseltamivir in preventing influenza in household contacts: a randomized controlled trial. *JAMA* 2001; 285: 748–754.
11. Clinical management of human infection with avian influenza A (H5N1) virus. www.who.int/entity/csr/disease/avian_influenza/guidelines.
12. Yuen KY, Wong SS. Human infection by avian influenza A H5N1. *Clin Microbiol Rev* 2005; 11: 189–199.
13. Bridgess CB, Matz JM, Seto WH. Risk of influenza A (H5N1) infection among health care workers exposed to patients with influenza A (H5N1), Hong Kong. *J Infect Dis* 2000; 181: 344–348.
14. Schultsz C, Dong VC, Chau NV. Avian influenza H5N1 and health care workers. *Emerg Infect Dis* 2003; 9: 1158–1159.
15. Pandemic influenza – science to policy. Report of the Royal Society. The Academy of Medical Sciences. www.royalsoc.ac.uk
16. Monto AS, McKimm-Breschikin JL, Macken C. Detection of influenza viruses resistant to neuraminidase inhibitors in global surveillance during the first 3 years of their use. *Antimicrob Agents Chemother* 2006; 50(7): 2395–2402.
17. European Medicines Agency: Updated review of influenza antiviral medicinal products for potential use during pandemic by the Committee for Medical Products for Human Use (CHMP) of the European Medicine Agency. www.emea.europa.eu.
18. Gubareva LV. Molecular mechanisms of influenza viruses resistance to neuraminidase inhibitors. *Virus Res* 2004; 103: 199–203.
19. McKimm-Breschikin JL. Resistance of influenza viruses to neuraminidase inhibitors. *Antivir Res* 2000; 46: 1–17.
20. Jackson HC, Roberts N, Wang ZM, Belshe R. Management of influenza: use of new antivirals and resistance in perspective. *Clin Drug Invest* 2000; 20: 447–454.
21. Whitley RJ, Hayden FG, Reisinger KS, Young N. Oral oseltamivir treatment of influenza in children. *J Pediatr Infect Dis* 2001; 30: 127–133.
22. Ward P, Small I, Smith J, Suter P, Dutkowski R. Oseltamivir (Tamiflu) and its potential for use in the event of an avian influenza pandemic. *J Antimicrob Chemother* 2005; 55: i5–i25.
23. Lackenby A, Hungnes O, Dudman SG, Meijer A, Paget WJ, Hay AJ, Zambon MC. Emergence of resistance to oseltamivir among influenza A (H1N1) viruses in Europe. *Eurosurveillance* 2008; 13: 1–3.
24. Nicoll A, Ciancio B, Kramarz P. Observed oseltamivir resistance in seasonal influenza viruses in Europe interpretation and potential implications. *Eurosurveillance* 2008; 13(5): 3–6.
25. Gubareva LV, Matrosovich MN, Brenner MK, Bethell RC. Evidence for zanamivir resistance in an immunocompromised child infected with influenza B virus. *J Infect Dis* 1998; 178: 1257–1262.
26. Reece PA. Neuraminidase inhibitor resistance in influenza viruses. *J Med Virol* 2007; 79: 1577–1586.
27. Varghese JN, Smith PW, Sollins SL, Blick TJ. Drug design against a shifting target: a structural basis for resistance to inhibitors in a variant of influenza virus neuraminidase. *Structure* 1998; 6: 735–746.
28. McKimm-Breschikin J, Selleck P, Usman T, Johnson M. Reduced sensitivity of influenza A (H5N1) to oseltamivir. *Emerg Infect Dis* 2007; 25: 3–12.
29. Yen HL, Hoffmann E, Taylor G, Scholtissek C. Importance of neuraminidase active site residues to the neuraminidase inhibitor resistance of influenza viruses. *J Virol* 2006; 80(17): 8787–8795.
30. www.who.int/csr/disease/avian_influenza/en/
31. Chotpitayasunonndh T, Ungchusak K, Hanshaoworakul W. Human disease from influenza A (H5N1), Thailand, 2004. *Emerg Infect Dis* 2005; 11: 1158–1159.
32. Tran TH, Nguen TL, Luong TS, Pham PM. Avian influenza A (H5N1) in 10 patients in Vietnam. *N Engl J Med* 2004; 350: 1179–1188.
33. Yen HL, Monto AS, Webster RG, Govorkova EA. Virulence may determine the necessary duration and dosage of oseltamivir treatment for highly pathogenic A/Vietnam/1203/04 influenza virus in mice. *Antimicrob Agents Chemother* 2001; 192: 665–672.
34. de Jong MD, Tran TT, Troung HK, VoMH, Smith GJ. Oseltamivir resistance during treatment of influenza A (H5N1) infection. *N Engl J Med* 2005; 353: 2667–2672.
35. Le QM, Kiso M, Someya K, Sakai T. Avian flu: isolation of drug-resistance H5N1 virus. *Nature* 2005; 437: 1108–1109.
36. WHO. Avian influenza situation in Egypt – update, 18 January 2007. www.who.int/csr/don/2007.

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Pytania dotyczące artykułu

1. Wskaż mechanizm działania inhibitorów neuraminidazy:
 - a) blokowanie kanałów wapniowych,
 - b) hamowanie aktywności enzymu odpowiedzialnego za uwalnianie wirionów potomnych z zakażonej komórki,
 - c) hamowanie aktywności enzymu odpowiedzialnego za przytwierdzenie wirusa do zakażonej komórki,
 - d) wszystkie powyższe.
2. W jakim czasie po wystąpieniu pierwszych objawów klinicznych grypy należy podać inhibitory neuraminidazy?
 - a) do 12 godzin,
 - b) do 24 godzin,
 - c) do 36–48 godzin,
 - d) czas podania nie ma znaczenia.
3. Zgodnie z rekomendacjami WHO lekiem z wyboru w leczeniu „grypy ptasiej”, wywołanej wirusem grypy typu A (H5N1) jest:
 - a) oseltamiwir,
 - b) zanamiwir,
 - c) peramiwir,
 - d) amantadyna.
4. Wskaż zdanie PRAWDZIWE dotyczące problemu oporności wirusów grypy na inhibitory neuraminidazy,
 - a) jak dotąd nie stwierdzono wirusów grypy typu H5N1 opornych na oseltamiwir,
 - b) nie obserwuje się narastania oporności wirusów grypy sezonowej na oseltamiwir,
 - c) nierozważne, zbyt częste stosowanie inhibitorów neuraminidazy może sprzyjać pojawianiu się wirusów opornych,
 - d) pacjenci, u których izoluje się wirusy odporne na inhibitory neuraminidazy zawsze mają cięższy przebieg choroby.
5. Zgodnie z zaleceniami WHO obecnie rekomendowanymi do leczenia i profilaktyki grypy sezonowej (pod warunkiem wykonania badań wirusologicznych) są:
 - a) amantadyna,
 - b) rymantadyna,
 - c) oseltamiwir,
 - d) zanamiwir,
 - e) peramiwir.

Polskie Towarzystwo Medycyny Rodzinnej

Aby zostać członkiem PTMR należy:

1. wypełnić deklarację członkowską (dostępna w sekretariacie lub na stronach internetowych)
2. uiścić **opłatę wpisową** (jednorazowo) w wysokości **20 PLN**
3. opłacać regularnie **składkę** (jeden raz w roku) – **60 PLN**

Nr konta PTMR: **47 1370 1356 0000 9540 3500 0110**

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Odpowiedzi na pytania do artykułu Anety Nitsch-Osuch i Lidii Brydak: Neuraminidase inhibitors resistance in influenza viruses – a current medical problem (s. 203–209).

Prawidłowe odpowiedzi na pytania:

1 – b, 2 – c, 3 – a, 4 – c, 5 – c