İNFLUENZA TEDAVİSİ

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KLİMİK Zonguldak Bölge Toplantısı
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Sunum planı

- Tedavide kullanılan antiviraller
- Kimlere tedavi verelim
- Ne zaman tedayiye başlayalım
- Diğer destekleyici tedaviler
- Gebelikte influenza tedavisi

- İnfluenza virus infeksiyonları ciddi salgınlara da neden olabilen önemli bir sağlık sorunudur.

- Yüksek riskli kişilerde artmış morbidite ve mortalite ile ilişkilidir.

- Tedavi kararı ve zamanının belirlenmesinde bazı durumlar dikkate alınmalıdır

İnfluenza Tedavisinde Kullanılan Antiviraller

- Nöraminidaz İnhibitörleri:

  * Zanamivir, Oseltamivir, Peramivir, Laninamivir

- Seçici İnfluenza Endonüklez İnhibitörü:

  * Baloxavir

- Adamantanlar:

  * Amantadin, Rimantadin

- **Nöraminidaz İnhibitörleri: Oseltamivir (Tamiflu), Zanamivir (Relenza)**

- Etki mekanizması ve yapı: Nöraminidaz aktivitesini inhibe eden siyalik asit analoglarıdır

- Nöraminidaz glikoproteini virusun enfekte hücreden çıkışını ve solunum yollarına penetrasyonunu kolaylaştırır

Oseltamivir

- Oral oseltamivir kolay emilir, gastrointestinal kanal, karaciğer ve kanda esterazlarla aktif metabolitlere metabolize olur
- Besinler emilimini geciktirir ancak biyoyararlanımını azaltmaz
- Bronkoalveoler sıvıda plazma düzeyinin %50'si saptanır
- Ön ilaç ve karboksilat formu böbrekten değişmeden glomerüler filtrasyon ve tübüler sekresyonla atılır
- En önemli yan etkisi: Bulantı, kusma (%10-15)
- Oseltamivir kullanımı sırasında Japon adolesanlarda geçici nöropsikiyatrik olaylar bildirilmiş (kendine zarar verme, deliryum)

MMWR/January 21, 2011/Vol. 60/No. 1

Aktaş F. Enfeksiyon Hastalıkları ve Mikrobiyolojisi, 2008 Nobel Tıp

Zanamivir

- Oral biyoyararlanımı çok az
- Oral inhalasyon için kuru toz içeren disk inhaler ile uygulanır, bu yolla %15'i akciğerlerde, kalanı orofarinksde depolanır
- Bronkospazma yol açabilir, altta yatan havayolu hastalığı olanlarda kullanımı önerilmez
- Altta yatan respiratuar ve kardiyak hastalığı bulunmayanlarda onay almıştır

MMWR/January 21, 2011/Vol. 60/No. 1
Aktaş F. Enfeksiyon Hastalıkları ve Mikrobiyolojisi, 2008 Nobel T

Zanamivir

- En sık saptanan yan etkiler: Diyare, bulantı, sinüzit, nazal bulgu ve semptomlar, bronşit, öksürük, baş ağrısı, baş dönmesi, kulak burun boğaz enfeksiyonları (her biri <%5)

- Allerjik reaksiyonlar, orofaringeal ve fasiyal ödem bildirilmiş

MMWR/January 21, 2011/Vol. 60/No. 1

Peramivir

- 2014 yılında FDA tarafından yetişkinlerde komplike olmayan influenza için onaylanmıştır
- 600 mg iv tek doz

Phase III Randomized, Double-Blind Study Comparing Single-Dose Intravenous Peramivir with Oral Oseltamivir in Patients with Seasonal Influenza Virus Infection[▽]†

Shigeru Kohno,[1]* Muh-Yong Yen,[2] Hee-Jin Cheong,[3] Nobuo Hirotsu,[4] Tadashi Ishida,[5] Jun-ichi Kadota,[6] Masashi Mizuguchi,[7] Hiroshi Kida,[8] and Jingoro Shimada[9] for the S-021812 Clinical Study Group

Second Department of Internal Medicine, Nagasaki University School of Medicine, Nagasaki,[1] Hirotsu Clinic[4] and St. Marianna University School of Medicine,[9] Kawasaki, Department of Respiratory Medicine, Kurashiki Central Hospital, Kurashiki,[5] Department of Internal Medicine II, Oita University Faculty of Medicine, Yufu,[6] Department of Developmental Medical Sciences, Graduate School of Medicine, University of Tokyo, Tokyo,[7] and Department of Disease Control, Graduate School of Veterinary Medicine, Hokkaido University, Sapporo,[8] Japan; Taipei City Hospital, National Yang-Ming University, Taipei, Taiwan[2]; and Department of Internal Medicine, Korea University Guro Hospital, Seoul, South Korea[3]

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Antiviral medications with activity against influenza viruses are important in controlling influenza. We compared intravenous peramivir, a potent neuraminidase inhibitor, with oseltamivir in patients with seasonal influenza virus infection. In a multinational, multicenter, double-blind, double-dummy randomized controlled study, patients aged ≥20 years with influenza A or B virus infection were randomly assigned to receive either a single intravenous infusion of peramivir (300 or 600 mg) or oral administration of oseltamivir (75 mg twice a day [b.i.d.] for 5 days). To demonstrate the noninferiority of peramivir in reducing the time to alleviation of influenza symptoms with hazard model analysis and a noninferiority margin of 0.170, we planned to recruit 1,050 patients in South Korea, Japan, and Taiwan. A total of 1,091 patients (364 receiving 300 mg and 362 receiving 600 mg of peramivir; 365 receiving oseltamivir) were included in the intent-to-treat infected population. The median durations of influenza symptoms were 78.0, 81.0, and 81.8 h in the groups treated with 300 mg of peramivir, 600 mg of peramivir, and oseltamivir, respectively. The hazard ratios of the 300- and 600-mg-peramivir groups compared to the oseltamivir group were 0.946 (97.5% confidence interval [CI], 0.793, 1.129) and 0.970 (97.5% CI, 0.814, 1.157), respectively. Both peramivir groups were noninferior to the oseltamivir group (97.5% CI, <1.170). The overall incidence of adverse drug reactions was significantly lower in the 300-mg-peramivir group, but the incidence of severe reactions in either peramivir group was not different from that in the oseltamivir group. Thus, a single intravenous dose of peramivir may be an alternative to a 5-day oral dose of oseltamivir for patients with seasonal influenza virus infection.

- 1091 yetişkin hasta İnfleunza A veya B ile enfekte
  - oral oseltamivir 75 mg 2x1
  - 300 mg veya 600 mg tek doz peramivir
- Ortalama influenza semptomlarının iyileşme süresi, 300 mg peramivir, 600 mg peramivir veya oseltamivir ile tedavi edilen gruplarda sırası ile 78, 81 ve 82 saat idi.
- Peramivir in her iki uygulaması da istatiksel olarak oseltamivirden daha az etkin değildi

Intravenous Peramivir for Treatment of Influenza A and B Virus Infection in High-Risk Patients[▽]†

Shigeru Kohno,[1]* Hiroshi Kida,[2] Masashi Mizuguchi,[3] Nobuo Hirotsu,[4] Tadashi Ishida,[5] Junichi Kadota,[6] Jingoro Shimada,[7] and the S-021812 Clinical Study Group

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Influenza virus infections are known to persist longer in patients with underlying diseases, including respiratory tract diseases, and tend to become complicated by secondary influenza-associated infections, such as pneumonia. To assess the efficacy and safety of the novel anti-influenza virus drug peramivir in high-risk patients, we conducted a clinical trial of patients with diabetes or chronic respiratory tract diseases and patients being treated with drugs that suppress immune function. In this multicenter, uncontrolled, randomized, double-blind study, peramivir was intravenously administered at 300 or 600 mg/day for 1 to 5 days, as needed. Efficacy was investigated in 37 patients (300 mg, $n = 18$ patients; 600 mg, $n = 19$ patients). The median durations of influenza illness were 68.6 h (90% confidence interval, 41.5 to 113.4 h) overall, 114.4 h (90% confidence interval, 40.2 to 235.3 h) in the 300-mg group, and 42.3 h (90% confidence interval, 30.0 to 82.7 h) in the 600-mg group. The hazard ratio for the 600-mg group compared to the 300-mg group was 0.497 (90% confidence interval, 0.251 to 0.984), and the duration of influenza illness was significantly shorter in the 600-mg group than in the 300-mg group. Among the 42 patients in the safety analysis set, adverse events occurred in 73.8% and adverse drug reactions in 33.3%. No adverse events were particularly problematic clinically, and all patients recovered quickly from all events. The measured blood drug concentrations showed no tendency toward accumulation. Drug accumulation with repeated doses was thus considered to be of little concern. Intravenous peramivir appears to offer a potentially useful treatment for high-risk patients in the future.

- KOAH, DM veya İmmunsupresyonu olan 37 yüksek riskli hasta
  * 18 tanesi 300 mg perinavir
  * 19 tanesi 600 mg perinavir iv uygulanmış

- 300 mg perinavir grubunda influenza semptomlarının ortanca iyileşme süresi 114,4 (güven aralığı %90) saat, 600 mg grubunda ise 42,3(güven aralığı %90) saat

- 600 mg alan grupta hastalık süresi belirgin olarak kısalmış

Baloxavir

- mRNA sentezini inhibe ederek influenza proliferasyonunu engelleyen *endonükleazın* selektif inhibitörüdür.
- ≥12 yaş komplike olmayan influenza için onay almıştır

The NEW ENGLAND JOURNAL of MEDICINE

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Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents

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- Komplike olmayan 1064 hasta
  * <80 kg ise 40 mg tek doz
  * ≥80 kg ise 80 mg tek doz
- Semptomların hafiflemesine kadar geçen medyan süre
  * plasebo alanlarda 80,2 saat
  * baloxavir alanlarda 53,7 saat ($p < 0,001$)

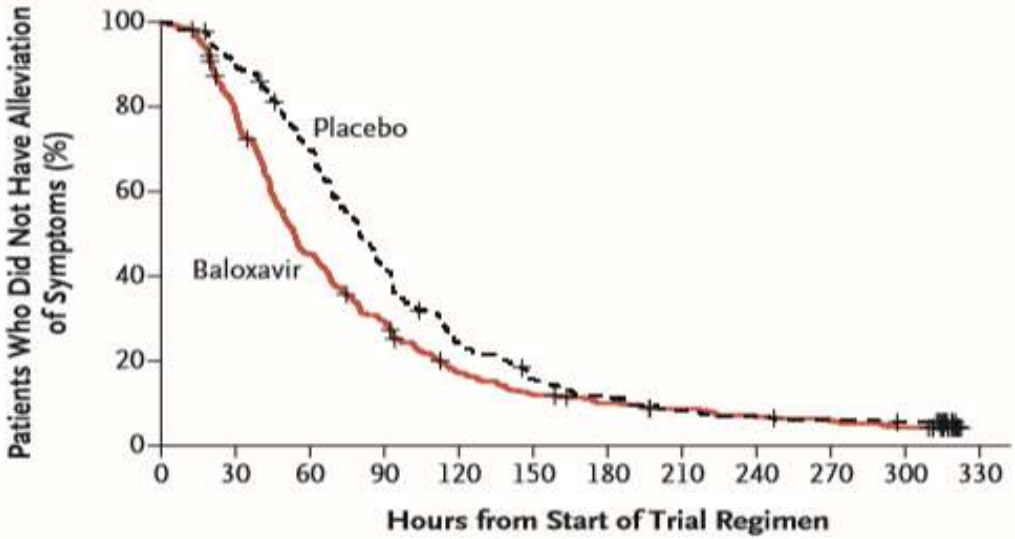

Figure 2. Kaplan–Meier Curves of the Time to Alleviation of Influenza Symptoms with Baloxavir versus Placebo in the Phase 3 Trial.

Shown are data for 455 patients assigned to baloxavir and 230 assigned to placebo (intention-to-treat infected population; 1 patient in each group did not have data that could be evaluated). The median time to alleviation of symptoms was 26.5 hours shorter in the baloxavir group (53.7 hours; 95% CI, 49.5 to 58.5) than in the placebo group (80.2 hours; 95% CI, 72.6 to 87.1) ($P<0.001$). Data from patients who did not have alleviation of symptoms were censored (tick marks) at the last observation time point.

- Aynı çalışmada oseltamivir 2x75 mg 5 gün ile karşılaştırılmış

  * semptomların hafifleme zamanı oseltamvir ile benzer bulunmuş

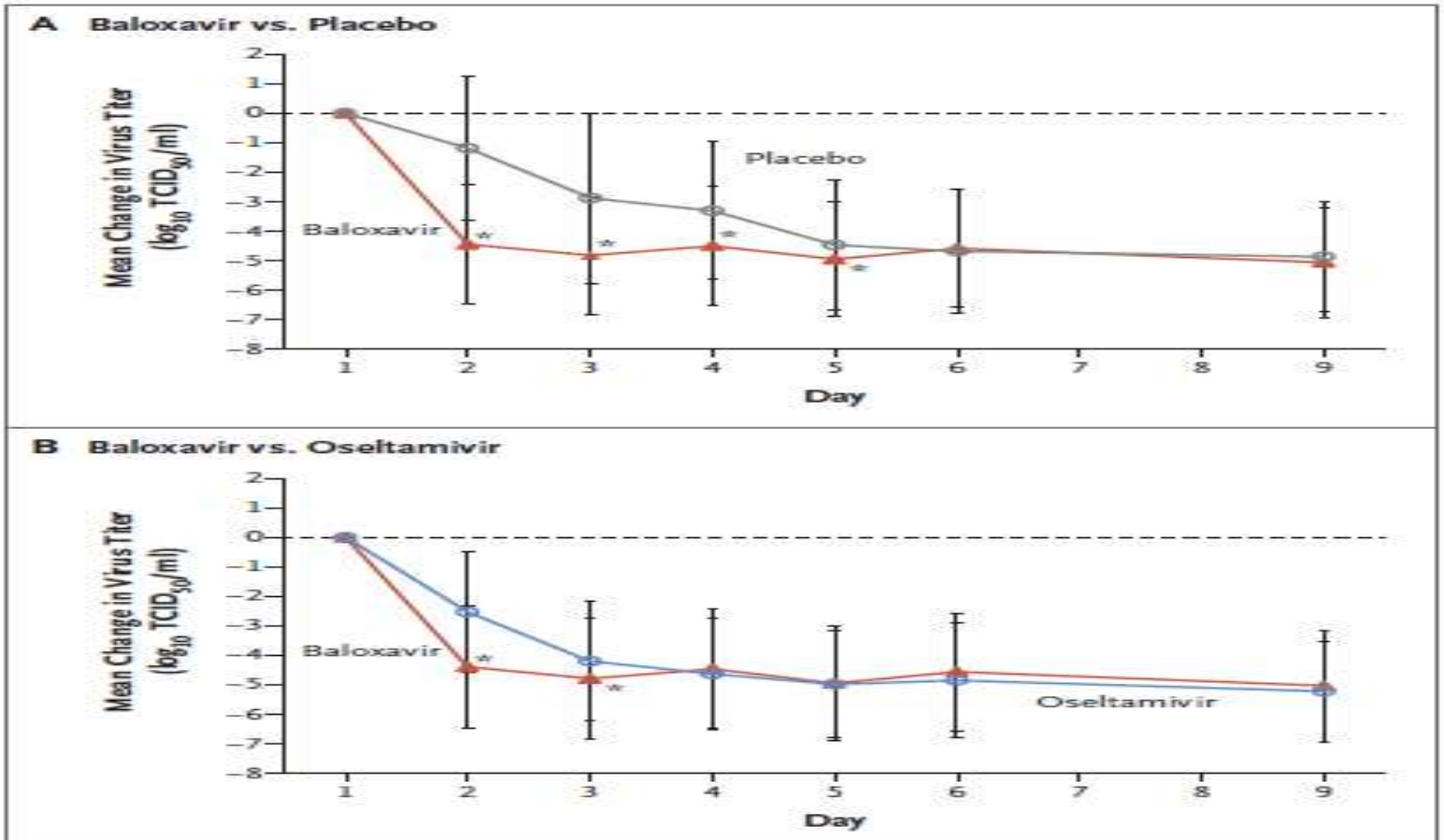

Figure 3. Change from Baseline in Influenza Infectious Viral Load over Time in the Phase 3 Trial.

Panel A shows the change from baseline (dashed line) in influenza infectious viral load over time in the baloxavir group (427 patients) and placebo group (210 patients). The mean (±SD) viral loads on day 1 (before the initiation of the trial regimen) were 5.79±1.87 and 5.56±1.89 log_{10} 50% tissue-culture infective dose ($TCID_{50}$) per milliliter in the baloxavir and placebo groups, respectively. Asterisks indicate a P value of less than 0.05 for the comparison with placebo. Panel B shows the change from baseline in influenza infectious viral load in adults 20 to 64 years of age in the baloxavir group (352 patients) and oseltamivir group (359 patients). The mean (±SD) viral loads on day 1 were 5.76±1.90 and 5.94±1.69 log_{10} $TCID_{50}$ per milliliter in the baloxavir and oseltamivir groups, respectively. Asterisks indicate a P value of less than 0.05 for the comparison with oseltamivir. In both panels, I bars indicate standard deviations.

- Diğer faz III çalışmasında (Capstone-2)
- Labaratuar olarak doğrulanmış 1158 yüksek riskli hasta (astım, koah, dm, ky, morbit obesite veya ≥65 yaş)
- Semptomların ortanca iyileşme süreleri
  * baloxavir grubunda 73 h
  * oseltamivir grubunda 81 h
  * placebo grubunda 102 h

LB16. Phase 3 Trial of Baloxavir Marboxil in High-Risk Influenza Patients (CAPSTONE-2 Study)

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Session: 213. Late Breaker Oral Abstracts: Influenza and Vaccines

Saturday, October 6, 2018: 10:30 AM

- Tek doz baloxavir semptomların iyileşme süresini plasebo alan gruba göre ortanca 29,1 saat kısaltmıştır. ($p<0,001$) fakat 5 gün oseltamivir tedavisi arasında fark bulunmamıştır.

- Baloxavir plasebo ile karşılaştırıldığında sistemik antibiyotik kullanımını ve infleunza ile ilişkili komplikasyonları belirgin azaltmıştır

Table 2 **Incidence of Adverse Events Occurring in At Least 1% of Subjects Receiving XOFLUZA in the Acute Uncomplicated Influenza Trials 1, 2, and 3**

Adverse Event	XOFLUZA (N = 1,440)	Placebo (N = 1,136)
Diarrhea	3%	4%
Bronchitis	3%	4%
Nausea	2%	3%
Sinusitis	2%	3%
Headache	1%	1%

- Kullanıma girdikten sonra hipersentivite reaksiyonları (anafilaksi, ürtiker, anjioödem, eritema multiforme) gözlenmiş

Laninamivir

- Japonya'da onay almış
- Laninamivir, H275Y mutasyonları içeren H1N1 virüsleri dahil olmak üzere, halen dolaşımda olan influenza A ve B virüslerine karşı etkilidir.
- 10 yaşından büyüklerde 40 mg tek doz inhalasyon şeklinde kullanılır.
- 10 yaşından küçüklerde 20 mg tek doz inhalasyon

Infectious Diseases (Fourth Edition) Volume 2, 2017, Pages 1318-1365.e2 Michael G. Ison, Frederick G. Hayden

TABLE 3 Recommended Dosage and Schedule of Influenza Antiviral Medications for Treatment and Chemoprophylaxis in Children for the 2019–2020 Influenza Season: United States

Medication	Treatment (5 d)	Chemoprophylaxis (10 d)[a]
Oseltamivir[b]		
Adults	75 mg, twice daily	75 mg, once daily
Children ≥12 mo (based on body wt)		
≤15 kg (≤33 lb)	30 mg, twice daily	30 mg, once daily
>15–23 kg (33–51 lb)	45 mg, twice daily	45 mg, once daily
>23–40 kg (>51–88 lb)	60 mg, twice daily	60 mg, once daily
>40 kg (>88 lb)	75 mg, twice daily	75 mg, once daily
Infants 9–11 mo[c]	3.5 mg/kg per dose, twice daily	3.5 mg/kg per dose, once daily
Term infants 0–8 mo[c]	3 mg/kg per dose, twice daily	3 mg/kg per dose, once daily for infants 3–8 mo Not recommended for infants <3 mo old because of limited safety and efficacy data in this age group
Preterm infants[d]		
<38 wk' postmenstrual age	1.0 mg/kg per dose, twice daily	—
38 through 40 wk' postmenstrual age	1.5 mg/kg per dose, twice daily	—
>40 wk' postmenstrual age	3.0 mg/kg per dose, twice daily	—
Zanamivir[e]		
Adults	10 mg (two 5-mg inhalations), twice daily	10 mg (two 5-mg inhalations), once daily
Children ≥7 y for treatment ≥5 y for chemoprophylaxis	10 mg (two 5-mg inhalations), twice daily	10 mg (two 5-mg inhalations), once daily
Peramivir		
Adults	One 600-mg IV infusion, given over 15–30 min	Not recommended
Children (2–12 y)	One 12 mg/kg dose, up to 600 mg maximum, via IV infusion for 15–30 min	Not recommended
Children (13–17 y)	One 600 mg dose, via IV infusion for 15–30 min	Not recommended
Baloxavir		
People ≥12 y who weigh more than 40 kg	40–80 kg: one 40-mg dose, orally ≥80 kg: one 80-mg dose, orally	Not recommended

Nöraminidaz inhibitörlerinin Karaciğer, Böbrek Yetmezliğinde Kullanımı ve İlaç Etkileşimleri

- Böbrek yetmezliği:
- * Zanamivir: Hafif-orta böbrek yetmezliğinde doz azaltılaması gerekmez
- Karaciğer yetmezliğinde kullanımlarına dair yeterli veri yok

- Probenesid'in oseltamivirin böbrek atılımını %50 azaltması dışında ilaç etkileşimleri yoktur

- Her iki ilaç için de yaşlılarda doz azaltılması gerekmez

MMWR/January 21, 2011/Vol. 60/No. 1 Aktaş F. Enfeksiyon Hastalıkları ve Mikrobiyolojisi, 2008 Nobel Tıp

Table 3. Recommended Oseltamivir and Peramivir Dose Adjustments for Treatment or Chemoprophylaxis of Influenza in Adult Patients with Renal Impairment or End Stage Renal Disease (ESRD) on Dialysis*

	Creatinine Clearance	Recommended Treatment Regimen	Recommended Chemoprophylaxis Regimen
Oral oseltamivir[1]	Creatinine clearance 61 to 90 mL/min	75 mg twice a day	75 mg once daily
	Creatinine clearance 31 to 60 mL/min	30 mg twice a day	30 mg once daily
	Creatinine clearance 11 to 30 mL/min	30 mg once daily	30 mg every other day
	ESRD Patients on Hemodialysis Creatinine clearance ≤10 mL/min	30 mg after every hemodialysis cycle. Treatment duration not to exceed 5 days[2]	30 mg after alternate hemodialysis cycles[3]
	ESRD Patients on Continuous Ambulatory Peritoneal Dialysis[4] Creatinine clearance ≤10 mL/min	A single 30 mg dose administered immediately after a dialysis exchange	30 mg once weekly immediately after dialysis exchange
Intravenous Peramivir (single dose)[5]	Creatinine clearance ≥50 mL/min	600 mg	N/A
	Creatinine clearance 30 to 49 mL/min	200 mg	N/A
	Creatinine clearance 10 to 29 mL/min	100 mg	N/A
	ESRD Patients on Hemodialysis	Dose administered after dialysis	

Tedavinin Yararları

- Antiviral tedavi alanlarda influenza semptomlarının 1,5-3 gün kısaldığı gösterilmiş.

- Antiviral tedavinin, influenza komplikasyonlarının şiddetini ve sıklığını, yaşlılar da dahil olmak üzere hastanede kalma süresini ve influenza ile ilişkili mortaliteyi azalttığı gösterilmiştir.

BMJ

BMJ 2014;348:g2545 doi: 10.1136/bmj.g2545 (Published 9 April 2014)

RESEARCH

Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments

OPEN ACCESS

Tom Jefferson *reviewer*[1], Mark Jones *senior research fellow (biostatistics)*[2], Peter Doshi *assistant professor*[3], Elizabeth A Spencer *nutritional epidemiologist*[4], Igho Onakpoya *research fellow in evidence-based practice and pharmacovigilance*[4], Carl J Heneghan *professor*[4]

BMJ

BMJ 2014;348:g2547 doi: 10.1136/bmj.g2547 (Published 9 April 2014)

RESEARCH

Zanamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments

OPEN ACCESS

Carl J Heneghan *professor of evidence based medicine*[1], Igho Onakpoya *research fellow in evidence based practice and pharmacovigilance*[1], Matthew Thompson *Helen D Cohen endowed professorship in family medicine*[2], Elizabeth A Spencer *nutritional epidemiologist*[1], Mark Jones *senior research fellow (biostatistics)*[3], Tom Jefferson *reviewer*[4]

- İmmünokompetan hastalarda yapılan bu çalışmalarda, antiviral tedavi alanlar arasında influenza komplikasyonlarında bir azalma olmadığı gösterildi

Tedavi Endikasyonları

- Şüpheli veya kanıtlanmış influenza enfeksiyonu olanlarda önceki influenza aşılama durumuna bakılmaksızın

  * influenza nedeniyle yatıyorsa (hastalık süresinden bağımsız)

  * ciddi ve ilerleyici hastalığı olan ayaktan hastalarda

  * influenza komplikasyon riski yüksek olan ayaktan hastalar

https://www.cdc.gov/flu/professionals/antivirals

- İDSA, influenza komplikasyon riski olmayan;

  * Hastalık süresinin kısaltmak için semptomların başlamasından sonra 48 saat içinde başvuran ayaktan hastalarda (C-I)

  * İnfluenza komplikasyonları açısından yüksek risk altındaki kişiler ile (özellikle immunsupresif olanların) ev içi teması olan ayaktan hastalara (C-III)

  * İnfluenza komplikasyon riski yüksek olan immunsupresif hastalara sağlık hizmeti veren hastaların da tedavi yönünden değerlendirilmesini önermektedir. (C-III)

Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials

Joanna Dobson, Richard J Whitley, Stuart Pocock, Arnold S Monto

- Şiddetli hastalığı olan veya komplikasyon riski yüksek olan bireyler antiviral tedavi almalıdır.
- Antiviral tedavi, mümkün olan en kısa sürede başlanılmalıdır.

Table 4. Persons Who Are at High Risk of Complications From Influenza

Persons at High Risk of Complications
Children aged <5 years, and especially aged <2 years
Adults aged ≥65 years
Persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematologic (including sickle cell disease), or metabolic disorders (including diabetes mellitus) or neurologic and neurodevelopment conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability [mental retardation], moderate to severe developmental delay, muscular dystrophy, or spinal cord injury)
Persons with immunosuppression, including that caused by medications or by HIV infection[a]
Women who are pregnant or postpartum (within 2 weeks after delivery)
Children and adolescents through 18 years who are receiving aspirin- or salicylate-containing medications and who might be at risk for experiencing Reye syndrome after influenza virus infection
American Indian/Alaska Native people[b]
Persons with extreme obesity (ie, body mass index ≥40 kg/m^2)
Residents of nursing homes and other chronic care facilities

- Asplenik hastalarda ise influenzanın ciddi ve komplikasyonla seyrettiği gösterilmemesine rağmen bu bireyler sekonder bakteriyel enfeksiyonlar açısından risk altında olduğundan antiviral tedavi önerilmektedir.

Hangi Antiviral

- Akut, komplike olmayan, ayaktan başvuru yapan hastalarda
  * oral oseltamivir
  * inhale zanamivir
  * i.v. Peramivir
  * oral baloxavir

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>40 kg (>88 lb)	75 mg, twice daily	75 mg, once daily
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Preterm infants[d]		
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38 through 40 wk' postmenstrual age	1.5 mg/kg per dose, twice daily	—
>40 wk' postmenstrual age	3.0 mg/kg per dose, twice daily	—
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Baloxavir		
People ≥12 y who weigh more than 40 kg	40–80 kg: one 40-mg dose, orally ≥80 kg: one 80-mg dose, orally	Not recommended

- Ciddi enfeksiyonu olan hospitalize hastalar (uzamış enfeksiyon ya da ybü yatması gereken hastalar) daha uzun tedavi süresine ihtiyaç duyabilir.

https://www.cdc.gov/flu/professionals/antivirals/avrec_ob.htm

Antiviral Tedavinin Zamanlaması

- Antiviral tedavi semptomlar başladıktan sonra 48 saat içinde başlanmalıdır.

- Test sonuçları beklenmemelidir.

- Ağır, komplike veya progresif hastalığı olan ve hospitalize olgularda hastalık başlangıcından >48 saat sonrasında başlanıldığında da fayda sağlamaktadır. (IDSA C-III)

Effects of oseltamivir treatment on duration of clinical illness and viral shedding, and household transmission of influenza virus

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Abstract

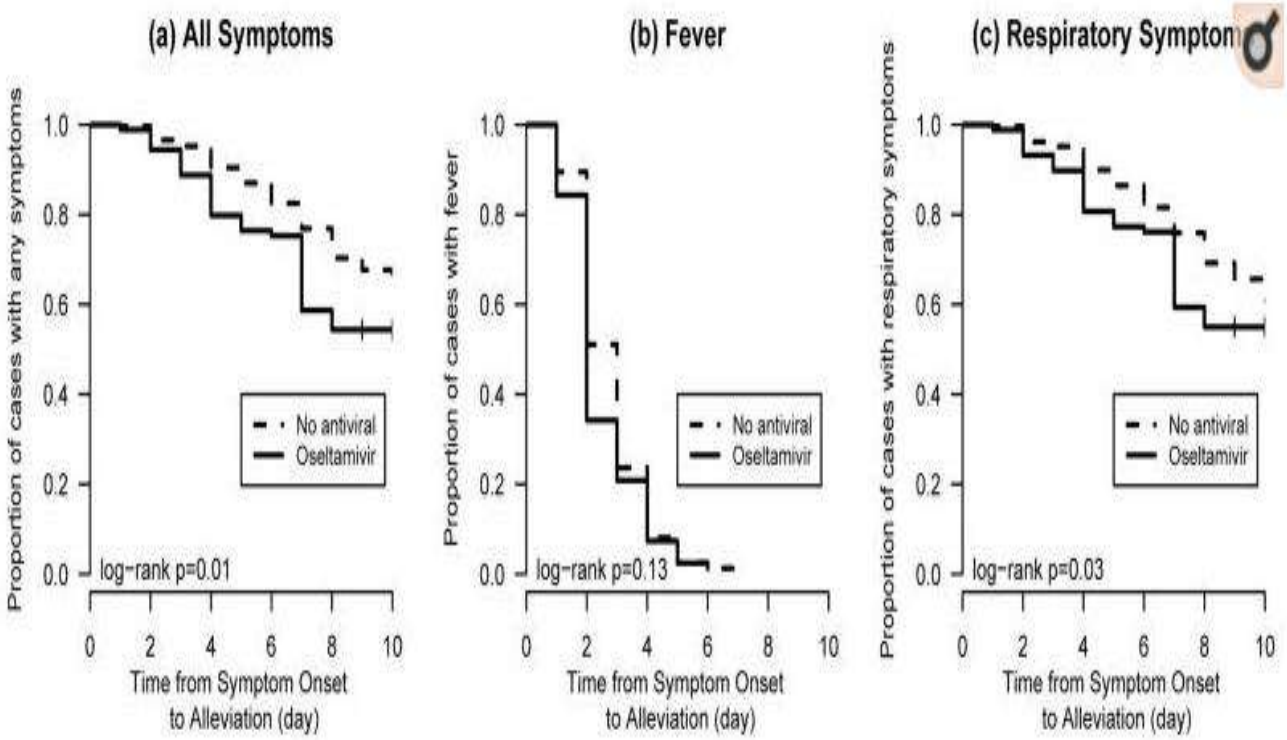
Background—Large clinical trials have demonstrated the therapeutic efficacy of oseltamivir against influenza. Here we assessed its indirect effectiveness in reducing household secondary transmission in an incident cohort of influenza index cases and their household members.

Methods—We recruited index outpatients whose rapid tests for influenza were positive in 2007 and 2008. Household contacts were followed for 7–10 days during 3–4 home visits to monitor symptoms. Nose and throat swabs were collected and tested for influenza by reverse transcription polymerase chain reaction (RT-PCR) or viral culture.

Results—We followed 384 index cases and their household contacts. Index cases who took oseltamivir within 24 hours of symptom onset halved the time to symptom alleviation (adjusted acceleration factor (AF) 0.56; 95% CI: 0.42, 0.76). Oseltamivir treatment was not associated with statistically significant reduction in the duration of viral shedding. Household contacts of index cases who had taken oseltamivir within 24 hours of onset had a non-statistically significant lower risk of developing laboratory-confirmed infection (adjusted odds ratio (OR) 0.54; 95% CI: 0.11, 2.57) and a marginally statistically significant lower risk of clinical illness (adjusted OR 0.52; 95% CI: 0.25, 1.08) compared to contacts of index cases who did not take oseltamivir.

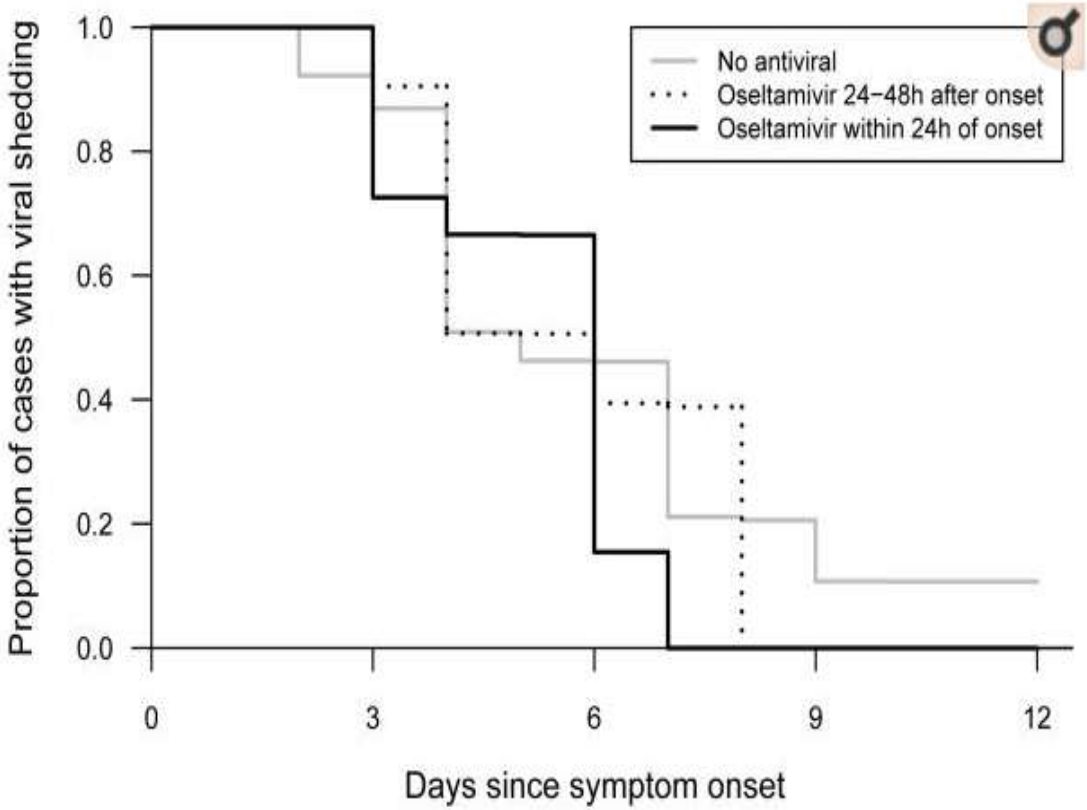
Conclusions—Oseltamivir treatment is effective in reducing the duration of symptoms but evidence for household reduction in transmission of influenza virus was inconclusive.

Figure 1



Kaplan Meier curves of time to resolution of (a) all symptoms (n=384), (b) fever (n=321), (c) respiratory symptoms (n=379) in index subjects with p-value of log-rank test.

Figure 2



Kaplan Meier curves of time to cessation of viral shedding in index subjects (n=392).

- Klinik çalışmalar ve gözlemsel veriler ile erken tedaviye başlamak hastalık semptomlarını ve ateşin süresini kısalttığı hatta olası komplikasyonları (otitis media, pnömoni, respiratuar yetmezlik) önlediği gösterilmiş.
- İlk 48 saat içinde başlanan Oseltamivir tedavisinin yatan hastalarda ölüm oranlarını azalttığı rapor edilmiş

- Konfirme edilmiş veya olası influenza enfeksiyonu düşünülen:

  * Hospitalize

  * Ağır, komplike, progresif hastalığı olan veya

  * İnfluenza komplikasyonları açısından yüksek riskli olguların mümkün olan en erken sürede antiviral(oseltamivir) ile tedavi edilmesi önerilmektedir

- Erken antiviral tedavi:

  ** Semptomların süresini ve şiddetini,*

  ** Hospitalizasyon ihtiyacını*

  ** İnfluenza komplikasyonlarını , influenzaya bağlı ağır hastalık, ölüm riskini*

  ** Antibiyotik kullanımını*

  ** Viral yayılım miktarını ve süresini*

azaltır.

Destekleyici Tedavi

- Semptomatik tedavi
- Ateş, baş ağrısı, miyalji gibi influenza semptomları için parasetamol veya nsaii kullanılmalıdır.
- Reye sendromu gelişme riski nedeniyle çocuklarda salisilat kullanımından kaçınılmaldır.

Antimikrobiyal Tedavi

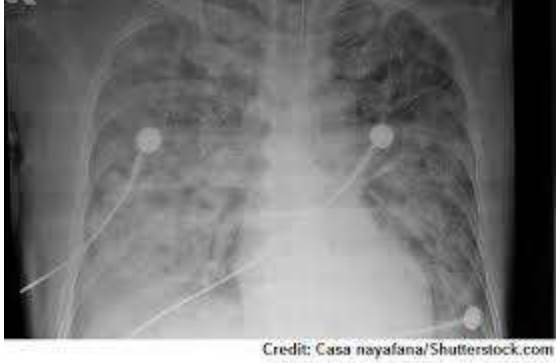
- Şiddetli hastalık(pnömoni, solunum yetmezliği, hipotansiyon ve ateş) ile başvuran şüpheli veya doğrulanmış influenza hastalarında olası bakteriyel koinfeksiyon değerlendirilmeli ve ampirik olarak tedavi edilmelidir.

- Antiviral ajanla tedavi edilenlerde, ilk iyileşmeden sonra kötüleşen hastalar da olası bakteriyel infeksiyon için değerlendirilmeli ve ampirik olarak tedavi edilmelidir.

- Üç ila beş günlük antiviral tedaviden sonra düzelmeyen hastalarda bakteriyel koinfeksiyon değerlendirilmelidir.

- İnvaziv bakteriyel ko-infeksiyon *Staflococcus aures, Streptococcus pneumoniae, Streptococcus pyogenes* (ve diğerleri) ile oluşabilir.

ARDS Yönetimi



- ARDS gelişen hastalara düşük tidal volüm ve düşük PEEP (positive end -expiratory pressure) uygulamalarını içeren akciğer koruyucu mekanik ventilasyon uygulanmalıdır.
- Bu önlemlerin uygulanmasına rağmen şiddetli hipoksemi devam eden hastalarda, ekstracorporeal membran oksijenasyonu (ECMO) veya eğilimli konumlandırma dahil olmak üzere belirli “kurtarma” stratejileri kullanılabilir.

Kortikosteroid kullanalım mı?

- Pek çok gözlemsel çalışma, kortikosteroid tedavisinin, uzamış viral yayılım, antiviral direnç ile bakteriyel ve fungal ko-infeksiyonlar ile ilişkili olduğunu göstermiş

- Kortikosteroid tedavisi; influenza, influenza ile ilişkili pnömoni, respiratuar yetmezlik veya ARDS de uygulanmamalıdır.(A-III)

Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenzaa

Direnç

- Oseltamivire dirençli olan Influenza A virüs varyantlarının ortaya çıkması ve küresel yayılması bir endişe kaynağıdır
- NAİ lerine dirençli influenza nadiren tespit edilir klinik olarak 2 şekilde karşımıza çıkar

  * Toplumda dolaşan, NAi lerine dirençli influenza ile infekte hasta olabilir (hasta tedaviye cevap vermeyebilir)

  * Tedavi sırasında direnç gelişebilir.(ilk yanıtın ardından klinik bozulma olabilir immunkompetan hastalarda nadirdir)

- Klinik olarak dirençten şüphelenildiğinde dökümante edilmelidir.Direncin en sık saptanan moleküler markerı influenza A (H1N1) pdm 09 nöraminidaz larında H275Y mutasyonudur.

- Oseltamivir direnci tespit edildiğinde kontrendike değilse inhale zanamivir tedavisine geçilmelidir.

- Oseltamivir direnci tespit edildiğinde tedavi seçenekleri sınırlıdır.

  NAİ dirençli influenza ile enfekte olmuş hastaların tedavisinde yol gösteren randomize kontrollü çalışma pek yoktur.

- H275Y mutasyonu, peramivirin, influenza virüsü enfeksiyonlarını bu mutasyonla tedavi etme etkinliğini de azaltır.

Open Access Full Text Article

REVIEW

Drug resistance in influenza A virus: the epidemiology and management

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Infection and Drug Resistance
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Number of times this article has been viewed

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Abstract: Influenza A virus (IAV) is the sole cause of the unpredictable influenza pandemics and deadly zoonotic outbreaks and constitutes at least half of the cause of regular annual influenza epidemics in humans. Two classes of anti-IAV drugs, adamantanes and neuraminidase (NA) inhibitors (NAIs) targeting the viral components M2 ion channel and NA, respectively, have been approved to treat IAV infections. However, IAV rapidly acquired resistance against both classes of drugs by mutating these viral components. The adamantane-resistant IAV has established itself in nature, and a majority of the IAV subtypes, especially the most common H1N1 and H3N2, circulating globally are resistant to adamantanes. Consequently, adamantanes have become practically obsolete as anti-IAV drugs. Similarly, up to 100% of the globally circulating IAV H1N1 subtypes were resistant to oseltamivir, the most commonly used NAI, until 2009. However, the 2009 pandemic IAV H1N1 subtype, which was sensitive to NAIs and has now become one of the dominant seasonal influenza virus strains, has replaced the pre-2009 oseltamivir-resistant H1N1 variants. This review traces the epidemiology of both adamantane- and NAI-resistant IAV subtypes since the approval of these drugs and highlights the susceptibility status of currently circulating IAV subtypes to NAIs. Further, it provides an overview of currently and soon to be available control measures to manage current and emerging drug-resistant IAV. Finally, this review outlines the research directions that should be undertaken to manage the circulation of IAV in intermediate hosts and develop effective and alternative anti-IAV therapies.

Keywords: influenza A virus, drug resistance, M2 ion channel inhibitors, neuraminidase inhibitors, oseltamivir, zanamivir

Gebelerde İnfluenza Tedavisi

Table 4. Persons Who Are at High Risk of Complications From Influenza

Persons at High Risk of Complications
Children aged <5 years, and especially aged <2 years
Adults aged ≥65 years
Persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematologic (including sickle cell disease), or metabolic disorders (including diabetes mellitus) or neurologic and neurodevelopment conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability [mental retardation], moderate to severe developmental delay, muscular dystrophy, or spinal cord injury)
Persons with immunosuppression, including that caused by medications or by HIV infection[a]
Women who are pregnant or postpartum (within 2 weeks after delivery)
Children and adolescents through 18 years who are receiving aspirin- or salicylate-containing medications and who might be at risk for experiencing Reye syndrome after influenza virus infection
American Indian/Alaska Native people[b]
Persons with extreme obesity (ie, body mass index ≥40 kg/m^2)
Residents of nursing homes and other chronic care facilities

- Gebelikte influenza geçirenlerde
  * Hospitalizayon
  * Yoğun bakıma yatış
  * ARDS gelişme riskinde artış
- Şüpheli veya doğrulanmış influenza olan gebelerin hemen antiviral tedavi alması gerekmektedir.

The Journal of Infectious Diseases

MAJOR ARTICLE

Benefit of Early Initiation of Influenza Antiviral Treatment to Pregnant Women Hospitalized With Laboratory-Confirmed Influenza

Ikwo K. Oboho,[1,2,a] Carrie Reed,[2] Paul Gargiullo,[2] Michelle Leon,[2] Deborah Aragon,[3] James Meek,[4] Evan J. Anderson,[5,6] Patricia Ryan,[7] Ruth Lynfield,[8] Craig Morin,[8] Marisa Bargsten,[9] Shelley M. Zansky,[10] Brian Fowler,[11] Ann Thomas,[12] Mary Lou Lindegren,[13] William Schaffner,[13] Ilene Risk,[14] Lyn Finelli,[2,a] and Sandra S. Chaves[2]

[1]Epidemic Intelligence Service, and [2]Influenza Division, Centers for Disease Control and Prevention, Atlanta, Georgia; [3]Colorado Department of Public Health and Environment, Denver; [4]Connecticut Emerging Infections Program, Yale School of Public Health, New Haven; [5]Department of Medicine, Emory University School of Medicine, and [6]Atlanta Veterans Affairs Medical Center, Georgia; [7]Maryland Department of Health and Mental Hygiene, Baltimore; [8]Minnesota Department of Health, St. Paul; [9]New Mexico Department of Health, Santa Fe; [10]New York State Department of Health, Albany; [11]Ohio Department of Health, Columbus; [12]Emerging Infections Program, Oregon Public Health Division, Portland; [13]Vanderbilt University School of Medicine, Nashville, Tennessee; and [14]Salt Lake County Health Department, Salt Lake City, Utah

(See the editorial commentary by Tita and Andrews on pages 505–6.)

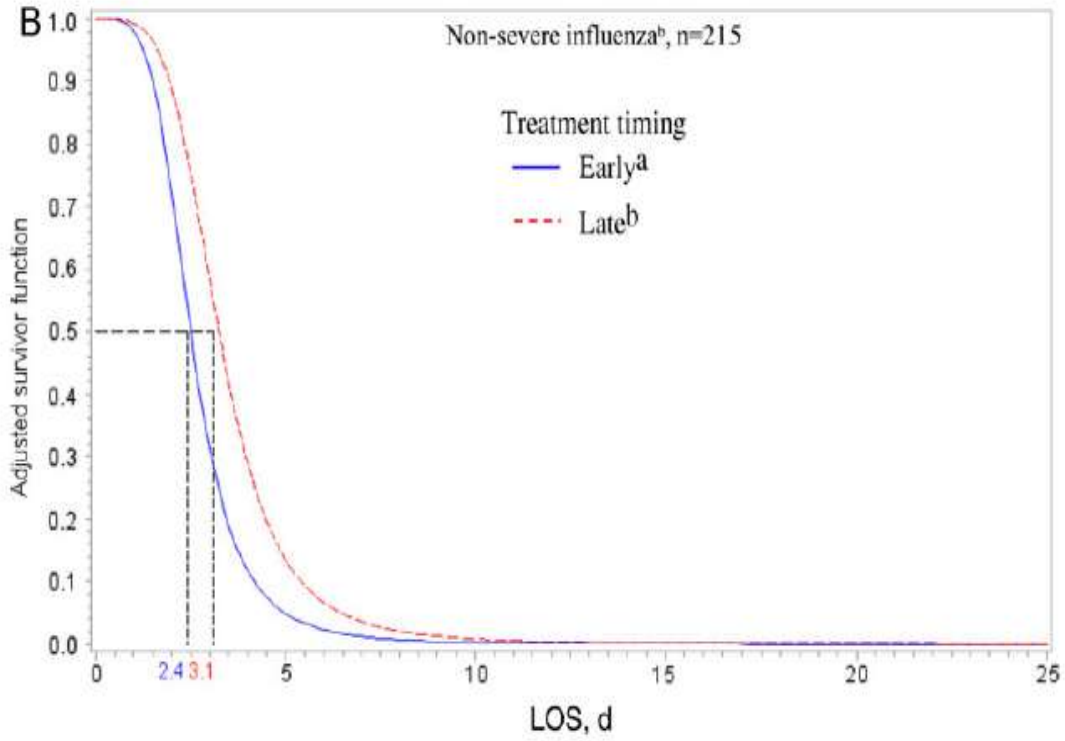
Background. We describe the impact of early initiation of influenza antiviral treatment among pregnant women hospitalized with laboratory-confirmed influenza during the 2010–2014 influenza seasons.

Methods. Severe influenza was defined as illness with ≥1 of the following: intensive care unit admission, need for mechanical ventilation, respiratory failure, pulmonary embolism, sepsis, or death. Within severity stratum, we used parametric survival analysis to compare length of stay by timing of antiviral treatment, adjusting for underlying conditions, influenza vaccination, and pregnancy trimester.

Results. Among 865 pregnant women, the median age was 27 years (interquartile range [IQR], 23–31 years). Most (68%) were healthy, and 85% received antiviral treatment. Sixty-three women (7%) had severe influenza, and 4 died. Severity was associated with preterm delivery and fetal loss. Women with severe influenza were less likely to be vaccinated than those without severe influenza (14% vs 26%; $P = .03$). Among women treated with antivirals ≤2 days versus those treated >2 days from illness onset, the median length of stay was 2.2 days (interquartile range [IQR], 0.9–5.8 days; n = 8) versus 7.8 days (IQR, 3.0–20.6 days; n = 7), respectively, for severe influenza ($P = .03$) and 2.4 days (IQR, 2.3–2.5 days; n = 153) versus 3.1 days (IQR, 2.8–3.5 days; n = 62), respectively, for nonsevere influenza ($P < .01$).

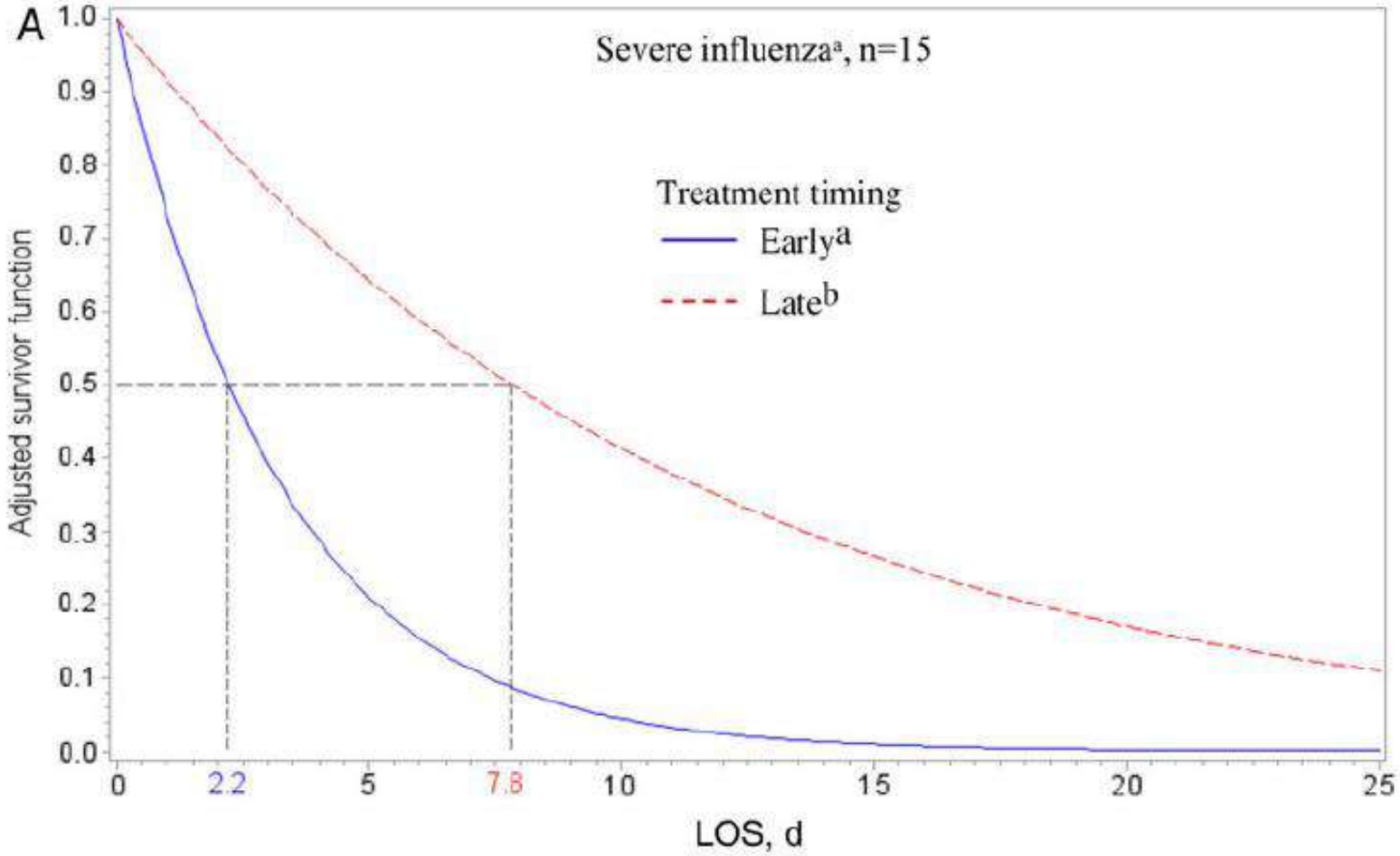
Conclusions. Early initiation of influenza antiviral treatment to pregnant women hospitalized with influenza may reduce the length of stay, especially among those with severe influenza. Influenza during pregnancy is associated with maternal and infant morbidity, and annual influenza vaccination is warranted.

Keywords. influenza; pregnancy; influenza antiviral treatment; length of stay; early antiviral treatment.



Treatment Timing	Women, No.	LOS, d, Median (IQR)	*P*
Early[a]	153	2.4 (2.3–2.5)	<.01
Late[b]	62	3.1 (2.8–3.5)	

Figure 1. Length of stay (LOS), by timing of treatment from illness onset, for 15 pregnant women with severe (*A*) and 215 with nonsevere (*B*) laboratory-confirmed influenza during the 2010–2014 influenza season who were hospitalized for >1 day and did not deliver or die during hospital stay. Data were obtained from the Influenza Hospitalization Surveillance Network. An exponential model was used for analysis of women with severe influenza, and a log-logistic model was used for analysis of women with nonsevere influenza. [a]≤2 days from illness onset; [b]>2 days from illness onset; [c]*P* values for LOS comparisons were calculated using the χ^2 test in a model adjusted for underlying medical condition, influenza vaccination status, and pregnancy trimester. Abbreviations: d, days; IQR, interquartile range.



Treatment Timing	Women, No.	LOS, d, Median (IQR)	*P*
Early[a]	8	2.2 (0.9–5.8)	.03
Late[b]	7	7.8 (3.0–20.6)	

- 865 gebe hasta

  * %68 sağlıklı %85 i antiviral tedavi almış

  * %7 ciddi influenza (4 ölüm)

- Tedaviye ilk 48 saat içinde başlananlar ile 48 saatten sonra başlananlar karşılaştırılmış

  * ciddi influenzada ortanca hastanede kalış süresi sırasıyla 2,2 ve 7,8 ($p=0.03$)

  * ciddi olmayan infleunzada ise yine sırasıyla 2,4 ve 3,1 ($p<0.01$)

Severe 2009 H1N1 Influenza in Pregnant and Postpartum Women in California

Louie JK, for the California Pandemic (H1N1) Working Group (California Dept of Public Health, Richmond; et al)

N Engl J Med 362:27-35, 2010

- Semptom başlangıcından 2 gün sonra başvuran gebe ve post-partum hastalarda ybü yatış ve mortalite riski yüksek bulunmuş

- *Gebelerde antiviral tedavi mümkün olan en kısa sürede başlanmalıdır. (özellikle ilk 48 saat içinde)*

Severity of 2009 Pandemic Influenza A (H1N1) Virus Infection in Pregnant Women

Andreea A. Creanga, MD, PhD, Tamisha F. Johnson, MD, Samuel B. Graitcer, MD, Laura K. Hartman, MD, Teeb Al-Samarrai, MD, MS, Aviva G. Schwarz, MPH, Susan Y. Chu, PhD, MSPH, Judith E. Sackoff, PhD, Denise J. Jamieson, MD, Anne D. Fine, MD, Carrie K. Shapiro-Mendoza, PhD, MPH, Lucretia E. Jones, MPH, Timothy M. Uyeki, MD, MPH, Sharon Balter, MD, Connie L. Bish, PhD, MPH, Lyn Finelli, DrPH, and Margaret A. Honein, PhD

OBJECTIVE: To examine 2009 H1N1 influenza illness severity and the effect of antiviral treatment on the severity of illness among pregnant women.

METHODS: We abstracted medical records from hospitalized pregnant (n=62) and nonpregnant (n=74) women with laboratory-confirmed 2009 H1N1 influenza in New York City, May through June 2009. We compared characteristics of pregnant and nonpregnant women and of severe and moderate influenza illness among pregnant women, with severe defined as illness resulting in intensive care admission or death.

RESULTS: The 2009 H1N1 hospitalization rate was significantly higher among pregnant than nonpregnant women (55.3 compared with 7.7 per 100,000 population). Eight pregnant (including two deaths) and 16 nonpregnant (including four deaths) cases were severe. Pregnant women represented 6.4% of hospitalized cases and 4.3% of deaths caused by 2009 H1N1 influenza. Only 1 in 30 (3.3%) pregnant women who received oseltamivir treatment within 2 days of symptom onset had severe illness compared with 3 of 14 (21.4%) and four of nine (44.4%) pregnant women who started treatment 3–4 days and 5 days or more after symptom onset, respectively (P=.002 for trend). Severe and moderate 2009 H1N1 influenza illness occurred in all pregnancy trimesters, but most women (54.8%) were in the third trimester. Twenty-two women delivered during their influenza hospitalization, and severe neonatal outcomes (neonatal intensive care unit admission or death) occurred among five of six (83.3%) women with severe illness compared with 2 of 16 (12.5%) women with moderate illness (P=.004).

CONCLUSION: Our findings highlight the potential for severe illness and adverse neonatal outcomes among pregnant 2009 H1N1 influenza-infected women and suggest the benefit of early oseltamivir treatment.

(Obstet Gynecol 2010;115:717–26)

LEVEL OF EVIDENCE: II

From the Epidemic Intelligence Service Program, Office of Workforce and Career Development; National Center for Chronic Disease Prevention and Health Promotion, Division of Reproductive Health; New York City Department of Health and Mental Hygiene; National Center for Immunization and Respiratory Diseases, Influenza Division; National Center on Birth Defects and Develop-

- Hastanede yatırılarak tedavi edilenlerde, ağır hastalarda ve gebelerde semptomların başlangıç süresi 48 saati geçse bile tedavinin yararlı olduğu gösterilmiş

- Tedaviye başlarken test sonuçları beklenmemelidir.
- Hızlı test sonucu negatif gelse bile tedavi ertelenmemelidir.
- Herhangi bir trimestrde tedavi başlanabilir.

ORIGINAL ARTICLE

Birth Defects Research | WILEY

Oseltamivir exposure in pregnancy and the risk of specific birth defects

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Funding information
U.S. National Vaccine Program Office (NVPO) in collaboration with the U.S. Biomedical Advanced Research and Development Authority (BARDA) and the U.S. Food and Drug Administration (FDA), Grant/Award Number: HHSP 233201600064C

Abstract

Background: Influenza during pregnancy contributes to maternal morbidity and mortality. Neuraminidase inhibitors, including oseltamivir, are recommended for treating women with influenza during pregnancy.

Methods: Data from the Slone Birth Defects Study from 2009 to 2015 were used to investigate associations between oseltamivir and specific birth defects. We classified exposures according to timing in pregnancy and examined 52 and 16 defects with early and potential late pregnancy etiology, respectively; we calculated crude odds ratios (ORs) and 95% confidence intervals (CIs) for defects with three or more exposures.

Results: Among 8,379 cases and 4,190 nonmalformed controls, we identified 79 and 42 oseltamivir exposures, respectively. The majority of defects had no exposures. ORs were elevated for several defects, but the CI excluded the null only for intestinal malrotation (OR: 10.7 [1.8, 45.2]; three exposures).

Conclusions: Largely null findings for specific defects are reassuring. The association with intestinal malrotation, while unstable, warrants further investigation.

KEYWORDS
birth defects, epidemiology, influenza, oseltamivir, pregnancy

Oseltamivir use in pregnancy: Risk of birth defects, preterm delivery, and small for gestational age infants

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Funding information
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Abstract

Background: Influenza infection during pregnancy increases risks for adverse outcomes for both mother and fetus. For this reason, treatment for infection or postexposure prophylaxis with a neuraminidase inhibitor, such as oseltamivir, may be needed.

Methods: Between 2009 and 2017, the Organization of Teratology Information Specialists (OTIS) MotherToBaby Pregnancy Studies enrolled pregnant women in the United States and Canada who were or were not treated with oseltamivir in a prospective cohort study. Data were collected on major birth defects, spontaneous abortion, preterm delivery, and small for gestational age birth size. Crude relative risks (RRs) or hazard ratios (HRs) were estimated together with 95% confidence intervals (CIs) for these outcomes.

Results: There were 716 subjects available for analysis; 112 were exposed to oseltamivir sometime in pregnancy and 604 were unexposed. 2/30 (6.7%) first-trimester-exposed pregnancies resulted in a fetus or infant with one or more major birth defects compared to 48/604 (7.9%) in the unexposed cohort (RR 0.84, 95% CI 0.19, 2.80). There were no spontaneous abortions reported. Risk of preterm delivery was not elevated in exposed versus comparison women (HR 0.65, 95% CI 0.26, 1.63). RRs for small for gestational age infants on weight, length, and head circumference following oseltamivir exposure anytime in pregnancy ranged from 0.70 to 1.30 with all 95% CIs including 1.

Conclusion: We found no evidence of increased risks with oseltamivir for any of the outcomes evaluated. While numbers are small, these data are reassuring for pregnant women who need to be treated for infection or for postexposure prophylaxis.

- Oseltamivir, zanamivir ve peramivirin gebelik kategorisi C.
- Birçok gözlemsel çalışmada bu ilaçların hamilelik esnasında güvenli olduğu, advers olayların veya istenmeyen yan etki riskini arttırmadığı gösterilmiş
- Gebelerde daha fazla çalışma olduğu, güvenli ve yararlı olduğu için 5 günlük oral oseltamivir tedavisi tercih edilen tedavidir. (ng ile uygulamada da yeterli düzeyde absorbsiyon sağlanmış)

Destekleyici Tedavi

- Semptomatik tedavi için parasetamol

Antibiyotik tedavisi

* Antibiyotikler bakteriyel pnömoni, otitis media veya sinüzit gibi bakteriyel komplikasyonlar için endikedir.

İmmunsupresif Hastalarda Tedavi

- Viral replikasyon uzayabilir, viral yayılım artabilir
- Tedavi sırasında veya sonrasında dirençli varyantlar ortaya çıkabilir

- İmmunsupresif hastalarda tedavi 10 gün veya daha fazla olmalıdır.
- Yüksek doz tedavi ile ilgili yeterli veri yoktur
- En yüksek fayda ilk 48 saat içinde tedavi başlanırsa gözlenir

Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza

Özet

- Risk faktörü olan kişiler kesinlikle antiviral tedavi almalıdır.
- Tedaviye, semptomlar başladıktan sonra 48 saat içinde başlanmalıdır.
- Ciddi hastalara 48 saat geçse bile tedavi verilmelidir.
- Gebelerde influenza normal popülasyona göre daha ağır, ciddi seyredebileceğinden oseltamivir 2x75 mg/gün şeklinde tedavi almalıdır.

Kaynaklar

- Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza
- https://www.cdc.gov/flu/professionals/index.htm
- https://www.uptodate.com/contents/treatment-of-seasonal-influenza-in-adults
- https://www.uptodate.com/contents/seasonal-influenza-and-pregnancy

- Teşekkürler…