

Web資料
（２）重症者へのオセルタミビル

2026-11-8

薬のチェック編集委員会

8.1 Antiviral therapies for patients with severe symptomatic influenza (suspected or confirmed)

8.1.1 Oseltamivir

Conditional recommendation for

In patients with suspected or confirmed severe influenza virus infection, we **suggest administering oseltamivir** (conditional recommendation, very low-quality evidence).

- Treatment should be administered as early as possible, and within 2 days of symptom onset.
- This recommendation applies to patients with novel influenza A virus infection associated with high mortality, or with an unknown risk of severe disease, even where they do not otherwise fulfil criteria for severe influenza.

8.1 重症かつ症状を伴うインフルエンザ（疑い例または確定例）患者に対する抗ウイルス療法

8.1.1 オセルタミビル

条件付き推奨重症

インフルエンザウイルス感染症が疑われる、または確定診断された患者に対して、**オセルタミビルの使用を推奨する**（条件付き推奨、エビデンスの質は極めて低い）。

•治療は可能な限り早期に、かつ症状の発現から2日以内に開始すべきである。
•本推奨は、高い死亡率を伴う新型インフルエンザA型ウイルス感染症の患者、あるいは重症化リスクが不明なインフルエンザ感染症の患者に適用される。これには、重症インフルエンザの診断基準を完全には満たさない患者も含まれる。

Table 8.3 Summary of findings for oseltamivir vs. standard care in patients with suspected or confirmed severe influenza virus infection

Outcome	Study results and measurements	Absolute effect estimates: Standard Care/ Placebo 標準治療/プラセボ	Absolute effect estimates: Oseltamivir オセルタミビル	Certainty of the evidence 証拠の確実性	Summary まとめ
Mortality (Seasonal influenza)	Relative risk: 0.53 (CI 95% 0.07 - 4.24) Based on data from 74 participants in 1 study	30 per 1000	16 per 1000	Very low Due to extremely serious imprecision[1] 著しく低い 顕著な不確実性のため	Whether oseltamivir reduces mortality is very uncertain. オセルタミビルが死亡を減らすかどうか極めて不確実（uncertain）
		Difference: 14 fewer per 1000 (CI 95% 28 fewer - 97 more)			

死亡率

死亡率差

1000人中14人少ない

相対リスク0.53(0.07-4.24)
74人を対象にした１試験の結果に基づく

95%信頼区間：28人少ない～97人多い可能性

Antivirals for treatment of severe influenza: a systematic review and network meta-analysis of randomised controlled trials

Gao et al Lancet 2024; 404: 753–63

Summary

Background The optimal antiviral drug for treatment of severe influenza remains unclear. To support updated WHO influenza clinical guidelines, this systematic review and network meta-analysis evaluated antivirals for treatment of patients with severe influenza.

Methods We systematically searched MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature, Global Health, Epistemonikos, and ClinicalTrials.gov for randomised controlled trials published up to Sept 20, 2023, that enrolled hospitalised patients with suspected or laboratory-confirmed influenza and compared direct-acting influenza antivirals against placebo, standard care, or another antiviral. Pairs of coauthors independently extracted data on study characteristics, patient characteristics, antiviral characteristics, and outcomes, with discrepancies resolved by discussion or by a third coauthor. Key outcomes of interest were time to alleviation of symptoms, duration of hospitalisation, admission to intensive care unit, progression to invasive mechanical ventilation, duration of mechanical ventilation, mortality, hospital discharge destination, emergence of antiviral resistance, adverse events, adverse events related to treatments, and serious adverse events. We conducted frequentist network meta-analyses to summarise the evidence and evaluated the certainty of evidence using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach. This study is registered with PROSPERO, CRD42023456650.

Findings Of 11 878 records identified by our search, eight trials with 1424 participants (mean age 36–60 years for trials that reported mean or median age; 43–78% male patients) were included in this systematic review, of which six were included in the network meta-analysis. The effects of oseltamivir, peramivir, or zanamivir on mortality compared with placebo or standard care without placebo for seasonal and zoonotic influenza were of very low certainty. Compared with placebo or standard care, we found low certainty evidence that duration of hospitalisation for seasonal influenza was reduced with oseltamivir (mean difference –1·63 days, 95% CI –2·81 to –0·45) and peramivir (–1·73 days, –3·33 to –0·13). Compared with standard care, there was little or no difference in time to alleviation of symptoms with oseltamivir (0·34 days, –0·86 to 1·54; low certainty evidence) or peramivir (–0·05 days, –0·69 to 0·59; low certainty evidence). There were no differences in adverse events or serious adverse events with oseltamivir, peramivir, and zanamivir (very low certainty evidence). Uncertainty remains about the effects of antivirals on other outcomes for patients with severe influenza. Due to the small number of eligible trials, we could not test for publication bias.

Interpretation In hospitalised patients with severe influenza, oseltamivir and peramivir might reduce duration of hospitalisation compared with standard care or placebo, although the certainty of evidence is low. The effects of all antivirals on mortality and other important patient outcomes are very uncertain due to scarce data from randomised controlled trials.

Funding World Health Organization.

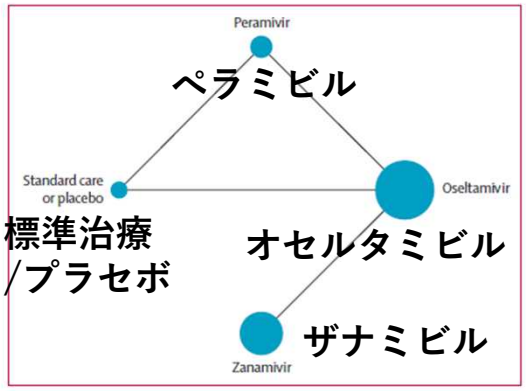


図2：死亡に関するネットワーク図
円の大きさは参加者数を表す。結ぶ線は直接比較を表す。線の太さは研究の数を表す。

	Study results and measurements	Seasonal influenza			
		Absolute effect estimate per 1000 patients	Absolute difference per 1000 patients (95% CI)	Certainty in effect estimates	Summary
Oseltamivir *vs* standard care or placebo	RR 0·53 (95% CI 0·07 to 4·24); based on data from 74 participants in one study	16 *vs* 30	–14 (–28 to 97)	Very low*	Whether oseltamivir reduces mortality in people with seasonal influenza is very uncertain

Appendix 8. Direct, indirect, and network treatment estimates

死亡率の直接,間接、ネットワークメタ解析

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8.1. Direct, indirect, and network treatment estimates for mortality

Comparison 比較	k 試験数	Prop 直接の割合	NMA (95% CI) ネットワークメタ解析	Direct (95% CI) 直接 (95%信頼区間)	Indirect (95% CI) 間接 (95%信頼区間)	RoR (95% CI) 比の比 (95%信頼区間)	z	Incoherence p-value 不一致性 P値
Oseltamivir vs. Peramivir	1	0.61	1.33 (0.11 to 15.87)	0.66 (0.03 to 15.79)	3.97 (0.08 to 207.32)	0.17 (0.00 to 26.45)	-0.7	0.487
Oseltamivir vs. Standard care/placebo	1	0.78	0.53 (0.07 to 4.24)	0.78 (0.07 to 8.17)	0.13 (0.00 to 11.50)	6.05 (0.04 to 969.21)	0.7	0.487
Oseltamivir vs. Zanamivir	1	1	0.91 (0.44 to 1.87)	0.91 (0.44 to 1.87)	NA	NA	NA	NA
Peramivir vs. Standard care/placebo	1	0.61	0.40 (0.03 to 4.72)	0.20 (0.01 to 4.69)	1.18 (0.02 to 61.91)	0.17 (0.00 to 26.45)	-0.7	0.487
Peramivir vs. Zanamivir	0	0	0.68 (0.05 to 9.01)	NA	0.68 (0.05 to 9.01)	NA	NA	NA
Zanamivir vs. Standard care/placebo	0	0	0.58 (0.06 to 5.29)	NA	0.58 (0.06 to 5.29)	NA	NA	NA

Comparison: treatment comparison; k: number of studies providing direct evidence; prop: direct evidence proportion; NMA: estimated treatment effect (RR) in network meta-analysis; direct: estimated treatment effect (RR) derived from direct evidence; indirect: estimated treatment effect (RR) derived from indirect evidence; RoR: Ratio of Ratios (direct versus indirect); z: z-value of test for disagreement (direct versus indirect); Incoherence p-value: p-value of test for disagreement (direct versus indirect). NA: not applicable.

オセルタミビルの死亡率比報告論文（1）

A Randomized Study Evaluating the Effectiveness of Oseltamivir Initiated at the Time of Hospital Admission in Adults Hospitalized With Influenza-Associated Lower Respiratory Tract Infections

直接死亡率比0.78の根拠

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Background. Influenza-associated hospitalizations result in high morbidity and mortality. We sought to determine if early empiric anti-influenza therapy improves outcomes of hospitalized patients with influenza-associated lower respiratory tract infections (I-LRTIs).

Methods. This was a randomized, unblinded, trial of adult patients hospitalized with I-LRTIs in Kentucky during 2009–2012. Patients were randomized to group A (standard of care) or group B (standard of care plus oseltamivir as early as possible but within 24 hours of enrollment). The primary outcome was development of clinical failure (composite variable including failure to reach clinical improvement within 7 days, transfer to intensive care 24 hours after admission, or rehospitalization or death within 30 days). Intent-to-treat (ITT) (all LRTI) and per-protocol (PP) (I-LRTI) analyses were done.

Results. A total of 1107 patients were enrolled and included in the ITT analysis, 556 in group A and 551 in group B. The median time from symptom onset to hospital admission was 5 days (interquartile range, 5) for both groups; oseltamivir was initiated median day 6 in group B. There was no difference in the development of clinical failure (group A, 25%, and group B, 24%; $P = .561$). In the PP analysis, 11 of 45 (24%) patients in group A and 4 of 29 (14%) patients in group B had clinical failure ($P = .414$).

Conclusions. Initiation of oseltamivir more than 5 days after illness onset did not reduce clinical failures among hospitalized patients with I- LRTIs. However, we did not enroll our projected sample size of I-LRTI.

Clinical Trials Registration. NCT01248715.

Keywords. oseltamivir; influenza; hospital.

ITT解析集団における死亡数と死亡率（%）

観察期間	死亡数（死亡率：%） 標準療法のみ N=556	死亡数（死亡率：%） オセルタミビル追加 N=551	P値
入院中	12(2)	14(3)	0.799
30日以内	27(5)	22(5)	0.671
1年以内	94(23)	84(22)	0.727

インフルエンザ感染集団における死亡数と死亡率（%）

観察期間	死亡数（死亡率：%） 標準療法のみ N=45	死亡数（死亡率：%） オセルタミビル追加 N=29	P値
入院中	1(2)	1(3)	>0.999
30日以内	2(5)	1(4)	>0.999
1年以内	6(19)	2(10)	0.616

死亡率比 0.78

インフルエンザ関連下気道感染症により入院した成人患者を対象とし、入院時にオセルタミビルを使用した有効性を評価する無作為化試験

要旨

背景：インフルエンザに関連する入院は、高い罹患率および死亡率を伴う。我々は、インフルエンザ関連下気道感染症（I-LRTI）で入院した患者に対し、早期に経験的抗インフルエンザ薬治療を行うことが転帰を改善するかどうかを検討した。方法：2009年から2012年にかけてケンタッキー州で実施された、I-LRTIにより入院した成人患者を対象とする無作為化非盲検試験である。患者をA群（標準治療）またはB群（標準治療に加え、登録後24時間以内に可能な限り早期のオセルタミビル投与）に無作為に割り付けた。**主要評価項目は「臨床的失敗」の発生**とした（臨床的失敗とは、7日以内に臨床的改善が得られない、入院24時間後に集中治療室へ転棟となる、あるいは30日以内に再入院または死亡する、といった事象を含む複合エンドポイントである）。
解析は、ITT（治療意図に基づく解析：すべての下気道感染症患者が対象）およびPP（プロトコル遵守に基づく解析：I-LRTI患者が対象）の両方で行った。結果：**計1107名の患者が登録され、ITT解析の対象となった（A群556名、B群551名）**。症状発現から入院までの期間中央値は両群とも5日（四分位範囲：5日）であり、B群におけるオセルタミビル投与開始時期の中央値は発症から6日目であった。臨床的失敗の発生率に差は認められなかった（**A群25%、B群24%、P = .561**）。PP解析では、臨床的失敗はA群で45名中11名（24%）、B群で29名中4名（14%）に認められた（P = .414）。
結論：発症から5日以上経過した後にオセルタミビル投与を開始しても、I-LRTIにより入院した患者における臨床的失敗を減少させることはできなかった。ただし、本研究では、当初予定していたサンプルサイズのI-LRTI患者を登録することはできなかった。
臨床試験登録：NCT01248715。

Early treatment with baloxavir marboxil in high-risk adolescent and adult outpatients with uncomplicated influenza (CAPSTONE-2): a randomised, placebo-controlled, phase 3 trial

Ison MG et al. Lancet Infect Dis. 2020 Oct;20(10):1204-1214. doi: 10.1016/S1473-3099(20)30004-9.

オセルタミビルの死亡率比報告論文（２） もう一つの死亡率比報告論文

Abstract

Background: Baloxavir marboxil (hereafter baloxavir), a selective inhibitor of influenza cap-dependent endonuclease, was approved in 2018 in the USA and Japan for the treatment of uncomplicated influenza in otherwise healthy individuals aged 12 years and older. We aimed to study the efficacy of baloxavir in outpatients at high risk of developing influenza-associated complications.

Methods: We did a double-blind, placebo-controlled and oseltamivir-controlled trial in outpatients aged 12 years and older in 551 sites in 17 countries and territories. Eligible patients had clinically diagnosed influenza-like illness, at least one risk factor for influenza-associated complications (eg, age older than 65 years), and a symptom duration of less than 48 h. Patients were stratified by baseline symptom score (≤14 vs ≥15), pre-existing and worsened symptoms at onset of illness compared with pre-influenza (yes or no), region (Asia, North America and Europe, or southern hemisphere), and weight (<80 kg vs ≥80 kg), and randomly assigned (1:1:1) via an interactive web-response system to either a single weight-based dose of baloxavir (40 mg for patients weighing <80 kg and 80 mg for patients weighing ≥80 kg; baloxavir group), oseltamivir 75 mg twice daily for 5 days (oseltamivir group), or matching placebo (placebo group). All patients, investigators, study personnel, and data analysts were masked to treatment assignment until database lock. The primary endpoint was time to improvement of influenza symptoms (TTIIS) in the modified intention-to-treat population, which included all patients who received at least one dose of study drug and had RT-PCR-confirmed influenza virus infection. Safety was assessed in all patients who receved at least one dose of study drug. This trial is registered with ClinicalTrials.gov, NCT02949011.

Findings: 2184 patients were enrolled from Jan 11, 2017, to March 30, 2018, and randomly assigned to receive baloxavir (n=730), placebo (n=729), or oseltamivir (n=725). The modified intention-to-treat population included 1163 patients: 388 in the baloxavir group, 386 in the placebo group, and 389 in the oseltamivir group. 557 (48%) of 1163 patients had influenza A H3N2, 484 (42%) had influenza B, 80 (7%) had influenza A H1N1, 14 patients had a mixed infection, and 28 had infections with non-typable viruses. The median TTIIS was shorter in the baloxavir group (73·2 h [95% CI 67·2 to 85·1]) than in the placebo group (102·3 h [92·7 to 113·1]; difference 29·1 h [95% CI 14·6 to 42·8]; p<0·0001). The median TTIIS in the oseltamivir group was 81·0 h (95% CI 69·4 to 91·5), with a difference from the baloxavir group of 7·7 h (-7·9 to 22·7). Adverse events were reported in 183 (25%) of 730 patients in the baloxavir group, 216 (30%) of 727 in the placebo group, and 202 (28%) of 721 in the oseltamivir group. Serious adverse events were noted in five patients in the baloxavir group, nine patients in the placebo group, and eight patients in the oseltamivir group; one case each of hypertension and nausea in the placebo group and two cases of transaminase elevation in the oseltamivir group were considered to be treatment related. Polymerase acidic protein variants with Ile38Thr, Ile38Met, or Ile38Asn substitutions conferring reduced baloxavir susceptibility emerged in 15 (5%) of 290 baloxavir recipients assessed for amino acid substitutions in the virus.

Interpretation: Single-dose baloxavir has superior efficacy to placebo and similar efficacy to oseltamivir for ameliorating influenza symptoms in high-risk outpatients. The safety of baloxavir was comparable to placebo. This study supports early therapy for patients at high risk of complications of influenza to speed clinical recovery and reduce complications.

Funding: Shionogi.

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Table 3. Study Outcomes in the Per-Protocol (Laboratory-Confirmed Influenza) Population

論文（1）

Variable	Group A (n = 45)	Group B (n = 29)	*P* Value
	標準治療	標準＋オセルタミビル	
Primary outcomes			
Clinical failure, n (%)	11 (24)	4 (14)	.414
Failure to reach clinical improvement within 7 days	5 (11)	1 (3)	.458
Transfer to intensive care unit after 24 hours of hospitalization	1 (2)	1 (3)	>.999
Rehospitalization 30 days	5 (14)	3 (12)	>.999
30-day mortality	2 (5)	1 (4)	>.999

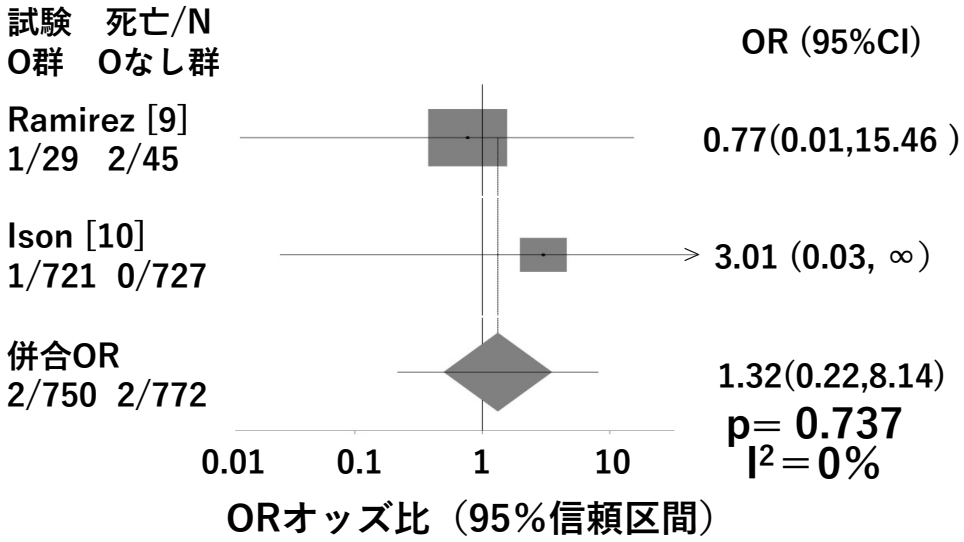
論文（2）

	Baloxavir group (n=730)	Placebo group (n=727)	Oseltamivir group (n=721)
Adverse events			
Any	183 (25%)	216 (30%)	202 (28%)
Reported in ≥2% of participants in any treatment group			
Bronchitis	21 (3%)	33 (5%)	30 (4%)
Sinusitis	14 (2%)	21 (3%)	22 (3%)
Diarrhoea	20 (3%)	21 (3%)	23 (3%)
Nausea	20 (3%)	29 (4%)	34 (5%)
Leading to withdrawal of study drug	5 (1%)	5 (1%)	4 (1%)
Serious adverse events (excluding death)	5 (1%)	9 (1%)	8 (1%)
Death*	0 *b	0	1 (<1%)

＊：オセルタミビル群の患者1例が、試験12日目に肺炎を発症し、38日目に死亡した。

*b：なお、この報告ではバロキサビル群に死亡例は報告されていないが、FDAの分析ではバロキサビル群でも１人が死亡した。

2試験のメタ解析結果



Ison報告の対照群はバロキサビル群の対照群でもあるので対照群を0/363.5としてメタ解析すると、併合オッズ比は1.16（0.17,7.85）、P=0.868,　I^2＝0%であった。
Peto ORは1.19(0.15,9.20),P=0.868, I^2＝0%であった。