The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 23, 2020 VOL. 383 NO. 4

Baloxavir Marboxil for Prophylaxis against Influenza in Household Contacts

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ABSTRACT

BACKGROUND

Baloxavir marboxil (baloxavir) is a polymerase acidic protein (PA) endonuclease inhibitor with clinical efficacy in the treatment of uncomplicated influenza, including in outpatients at increased risk for complications. The postexposure prophylactic efficacy of baloxavir in the household setting is unclear.

METHODS

We conducted a multicenter, double-blind, randomized, placebo-controlled trial to evaluate the postexposure prophylactic efficacy of baloxavir in household contacts of index patients with confirmed influenza during the 2018–2019 season in Japan. The participants were assigned in a 1:1 ratio to receive either a single dose of baloxavir or placebo. The primary end point was clinical influenza, as confirmed by reverse-transcriptase–polymerase-chain-reaction testing, over a period of 10 days. The occurrence of baloxavir-selected PA substitutions associated with reduced susceptibility was assessed.

RESULTS

A total of 752 household contacts of 545 index patients were randomly assigned to receive baloxavir or placebo. Among the index patients, 95.6% had influenza A virus infection, 73.6% were younger than 12 years of age, and 52.7% received baloxavir. Among the participants who could be evaluated (374 in the baloxavir group and 375 in the placebo group), the percentage in whom clinical influenza developed was significantly lower in the baloxavir group than in the placebo group (1.9% vs. 13.6%) (adjusted risk ratio, 0.14; 95% confidence interval [CI], 0.06 to 0.30; P<0.001). Baloxavir was effective in high-risk, pediatric, and unvaccinated subgroups of participants. The risk of influenza infection, regardless of symptoms, was lower with baloxavir than with placebo (adjusted risk ratio, 0.43; 95% CI, 0.32 to 0.58). The incidence of adverse events was similar in the two groups (22.2% in the baloxavir group and 20.5% in the placebo group). In the baloxavir group, the viral PA substitutions I38T/M or E23K were detected in 10 (2.7%) and 5 (1.3%) participants, respectively. No transmission of these variants from baloxavir-treated index patients to participants in the placebo group was detected; however, several instances of transmission to participants in the baloxavir group could not be ruled out.

CONCLUSIONS

Single-dose baloxavir showed significant postexposure prophylactic efficacy in preventing influenza in household contacts of patients with influenza. (Funded by Shionogi; Japan Primary Registries Network number, JapicCTI-184180.)

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This article was published on July 8, 2020, at NEJM.org.

N Engl J Med 2020;383:309-20.
DOI: 10.1056/NEJMoa1915341

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Households and other close-contact settings such as dormitories and schools are important sites for seasonal and pandemic transmission of influenza virus.[1,2] School-age children often introduce the virus into households, with subsequent spread to younger siblings and adults.[3] Adherence to nonpharmaceutical interventions such as handwashing and wearing a face mask can reduce the risk of transmission somewhat in these settings if these measures are initiated quickly.[4-7] In addition, previous household-based randomized, controlled trials have shown that postexposure antiviral prophylaxis with adamantanes (when circulating viruses were susceptible) or neuraminidase inhibitors is effective in reducing the risk of influenza among contacts.[8-14] However, when rimantadine was used both for the treatment of the household index case and for postexposure prophylaxis, drug-resistant influenza A virus emerged rapidly and was transmitted to contacts, causing prophylaxis failures.[15] Transmission of resistant virus was not observed when either oral oseltamivir or inhaled zanamivir was used for both treatment and prophylaxis within households.[8,10]

Baloxavir marboxil (baloxavir), a prodrug of the cap-dependent endonuclease inhibitor baloxavir acid ("cap" refers to a 7-methyl guanosine that is added to the 5′ end of the host messenger RNA strand), was approved as a single-dose treatment for uncomplicated influenza A and B in Japan and the United States in 2018 and was recently approved in the United States for the treatment of influenza in patients who were at risk for complications. Baloxavir treatment within 2 days after the onset of illness shortened the duration of illness by approximately 1 day as compared with placebo and showed superior antiviral efficacy to both placebo and oseltamivir.[16,17] However, variant viruses with amino acid substitutions in the polymerase acidic protein (PA) have emerged after baloxavir treatment. Position PA I38 substitutions (T, M, S, or F) are most common, and a virus with such a substitution is 10 to more than 420 times less susceptible to baloxavir in vitro than is wild-type virus; a virus with a substitution at other positions, such as PA E23, PA A37, or PA E199, is 3 to 10 times less susceptible.[18-20] PA I38X–substituted viruses have emerged in 2.2 to 9.8% of baloxavir-treated adolescents and adults[16,17] and in 19.3 to 23.4% of baloxavir-treated children.[21,22] The detection of PA I38X variant viruses has been associated with prolongation of infectious virus replication[19,21,22] and potential transmissibility, including one instance of household transmission.[23,24]

In a multicenter, double-blind, randomized, placebo-controlled clinical trial, we assessed the efficacy of postexposure prophylaxis with a single dose of baloxavir for the prevention of influenza in household contacts. Because the majority of index patients were children who had been treated with baloxavir or a neuraminidase inhibitor, the trial also allowed for an assessment of the risks of the emergence and transmission of influenza viruses with reduced susceptibility to baloxavir.

Methods

Trial Design and Oversight

Index patients, who were defined as those having the first documented case of influenza in a household, were identified at 52 primary care clinics in Japan from November 2018 through March 2019 (see the Supplementary Appendix, available with the full text of this article at NEJM.org). These patients were identified on the basis of a positive rapid influenza diagnostic test and received antiviral treatment (baloxavir or neuraminidase inhibitor) at the discretion of each investigator.

The trial was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council for Harmonisation. The protocol was approved by an institutional review board at each trial site. All the index patients and participating household contacts (or their legal representatives) provided written informed consent. The sponsor (Shionogi, the manufacturer of baloxavir) designed the trial, and the authors' access to the data was not restricted by confidentiality agreements. Data were compiled by the sponsor and analyzed by a statistician employed by the sponsor. The sponsor and authors vouch for the completeness and accuracy of the data and for the adherence of the trial to the protocol, available at NEJM.org.

Trial Population

Eligible participants were household contacts who were well (defined as no influenza symptoms and an axillary temperature of <37.0°C) and had lived

in the same household as the index patient for at least 48 hours before enrollment. Other inclusion and exclusion criteria are provided in the Supplementary Appendix.

TREATMENT AND RANDOMIZATION

Participants were randomly assigned in a 1:1 ratio to receive a single, weight-based oral dose of baloxavir or matching placebo. Randomization was performed on an individual basis with the use of an interactive Web-response system (see the Supplementary Appendix). The randomization used the stochastic minimization method for balancing the following three factors: time from onset of illness in the index patient to informed consent of the participant (<24 hours or ≥24 hours), treatment of index patient (baloxavir or neuraminidase inhibitor), and participant's age (<12 years or ≥12 years).

CLINICAL, VIROLOGIC, AND LABORATORY MONITORING

The axillary temperature was recorded twice daily from screening until day 10. Participants who were 12 years of age or older assessed themselves for seven symptoms associated with influenza (cough, sore throat, headache, nasal discharge or congestion, feverishness or chills, muscle or joint pain, and fatigue) on a 4-point rating scale (0, absent; 1, mild; 2, moderate; and 3, severe). For participants younger than 12 years of age, the participant's guardian assessed two symptoms (cough and nasal discharge or congestion) on the same 4-point rating scale.

Nasopharyngeal swabs were obtained from participants before the dose of baloxavir or placebo was administered (day 1) and again on day 5 (in the window of days 3 through 7) and day 11 (in the window of days 11 through 14). In addition, participants were instructed to visit the trial site to undergo swabbing if fever and moderate or severe influenza-like symptoms developed. Swab specimens were tested for influenza virus and virus type or subtype by means of reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay and used for direct sequencing of the PA and hemagglutinin (HA) genes. Blood samples were obtained on day 1 before the dose was administered and on day 5 (in the window of days 3 through 7) and day 15 (in the window of days 15 through 22) for safety monitoring. Hemagglutination inhibition (HAI) antibody titers were assessed on day 1 and between days 15 and 22. Details are provided in the Supplementary Appendix.

EFFICACY END POINTS

The primary efficacy end point was laboratory-confirmed clinical influenza, defined as RT-PCR positivity for influenza virus RNA and the presence of both fever (axillary temperature, ≥37.5°C) and at least one respiratory symptom of moderate or greater severity during the period from day 1 to day 10. The primary end point was evaluated in the modified intention-to-treat population (defined as all the participants who had undergone randomization and for whom postenrollment data regarding symptom and virologic features were available), in participants who had negative results on RT-PCR assay at baseline and had contact with an RT-PCR–positive index patient, and in prespecified subgroups (see the Supplementary Appendix).

Key secondary clinical end points were RT-PCR–confirmed illness, defined as RT-PCR positivity for influenza virus RNA plus a body temperature of at least 37.5°C or at least one moderate or severe symptom, and RT-PCR–confirmed influenza virus infection regardless of fever and symptoms. Post hoc analyses also examined the percentages of participants with any evidence of infection, infection with illness, or asymptomatic infection, according to seroconversion (a quadrupling of the HAI antibody titer) or RT-PCR positivity. The key safety end points were the clinical adverse events and abnormal laboratory values (see the Supplementary Appendix).

STATISTICAL ANALYSIS

The planned required sample was 748 participants on the basis of the assumptions that the risk ratio would be 0.4, that the percentage of participants with clinical influenza in the placebo group would be 10%,[13,14] and that 374 participants in each group would provide the trial with 90% power to detect the superiority of baloxavir prophylaxis over placebo.

Between-group comparisons were conducted with the modified Poisson regression approach[25] with the aforementioned randomization factors (time from onset of illness, type of antiviral treatment of index patient, and age of the participant

Table 1. Demographic and Baseline Characteristics of Index Patients and Participants.*

Characteristic	Index Patients (N=545)†	Household Contacts	
		Baloxavir Marboxil (N=374)	Placebo (N=375)
Age			
Mean — yr	11.3±12.5	33.5±15.8	33.6±17.0
Distribution — no. (%)			
<6 yr	160 (29.4)	16 (4.3)	23 (6.1)
6–11 yr	241 (44.2)	55 (14.7)	48 (12.8)
12–19 yr	93 (17.1)	14 (3.7)	23 (6.1)
20–64 yr	43 (7.9)	281 (75.1)	266 (70.9)
≥65 yr	8 (1.5)	8 (2.1)	15 (4.0)
No. of persons in household, excluding index patient	3.2±1.1	—	—
No. of household participants who underwent randomization	1.4±0.7	—	—
Male sex — no. (%)	290 (53.2)	77 (20.6)	85 (22.7)
Influenza vaccination within previous 6 mo — no. (%)	170 (31.2)	131 (35.0)	124 (33.1)
Presence of underlying high-risk factors in household contacts — no. (%)	—	46 (12.3)	52 (13.9)
Occupation — no. (%)			
Student	472 (86.6)	81 (21.7)	89 (23.7)
Worker	34 (6.2)	223 (59.6)	208 (55.5)
Neither	39 (7.2)	70 (18.7)	78 (20.8)
Current smoking — no. (%)	8 (1.5)	38 (10.2)	37 (9.9)
Baseline influenza virus subtype as determined by RT-PCR assay — no. (%)			
A(H1N1)pdm09	255 (46.8)	2 (0.5)	11 (2.9)
A(H3N2)	265 (48.6)	16 (4.3)	16 (4.3)
A, not determined	1 (0.2)	8 (2.1)	9 (2.4)
B	5 (0.9)	0	0
Mixed infection	12 (2.2)	0	0
Negative	7 (1.3)	348 (93.0)	339 (90.4)
Virus titer in index patients — $\log_{10}$ $TCID_{50}$/ml	5.40±1.99	—	—
Antiviral treatment in index patients — no. (%)			
Baloxavir	287 (52.7)	—	—
Oseltamivir	171 (31.4)	—	—
Neuraminidase inhibitor other than oseltamivir‡	87 (16.0)	—	—
No. of households	—	327	330
Percentage of household contacts assigned to a trial group per household			
Mean	—	82.5±25.0	83.4±23.9
Median (interquartile range)	—	50 (50.0–100.0)	50 (50.0–100.0)

Table 1. (Continued.)

Characteristic	Index Patients (N=545)†	Household Contacts	
		Baloxavir Marboxil (N=374)	Placebo (N=375)
Relation to index patient — no. (%)			
Parent	—	267 (71.4)	252 (67.2)
Sibling	—	83 (22.2)	89 (23.7)
Child	—	5 (1.3)	10 (2.7)
Spouse	—	13 (3.5)	14 (3.7)
Other	—	6 (1.6)	10 (2.7)
<24 Hr from onset of influenza symptoms in index patient to receipt of informed consent from participant — no. (%)	—	272 (72.7)	271 (72.3)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. NA denotes data not available, RT-PCR reverse-transcriptase–polymerase-chain-reaction, and $TCID_{50}$ the 50% tissue-culture infectious dose.
† All index patients who had at least one household contact who underwent randomization in the trial were included. The index patient was counted for each enrolled participant in that household (Table S1). Nucleotide sequencing of polymerase acidic protein region was conducted on baseline samples obtained from 114 index patients corresponding to household contacts who had positive results on RT-PCR assay after receipt of the dose.
‡ This category included inhaled zanamivir, inhaled laninamivir, and intravenous peramivir.

[continuous variable]) as covariates. For protective efficacy, the adjusted risk ratio with baloxavir as compared with placebo and the 95% confidence interval were determined.

All the statistical tests were performed at the two-sided significance level of 0.05. No adjustment for multiple comparisons was made in secondary efficacy end-points analyses, subgroup analyses, and post hoc analyses. For these outcomes, 95% confidence intervals are reported, without P values. The confidence intervals have not been adjusted for multiplicity and should not be used to infer treatment effects. All the analyses were performed with the use of SAS software, version 9.4 (SAS Institute).[26]

RESULTS

INDEX PATIENTS

Of the 545 index patients, 73.6% were younger than 12 years of age, and 95.6% had influenza A virus infection, with similar percentages of detection of A(H1N1)pdm09 and A(H3N2) (Table 1). All the index patients received treatment with antiinfluenza drugs, including baloxavir in 52.7%, oseltamivir in 31.4%, and another neuraminidase inhibitor in 16.0%. The characteristics of the index patients were similar in the baloxavir group and the placebo group (Table S1 in the Supplementary Appendix).

PARTICIPANTS

A total of 752 household participants underwent randomization, 749 of whom (99.6%) constituted the modified intention-to-treat population (Fig. S1). The characteristics of the participants at baseline were similar in the two groups (Table 1). Overall, 19.0% of the participants were younger than 12 years of age, 3.1% were 65 years of age or older, 13.1% had at least one risk factor for influenza-related complications, and 66.0% were unvaccinated against influenza in the current season. Most of the participants (72.5%) received baloxavir or placebo within 24 hours after the onset of illness in the index patients. A total of 26 participants (7.0%) in the baloxavir group and 36 (9.6%) in the placebo group were RT-PCR–positive for influenza at baseline. In most instances,

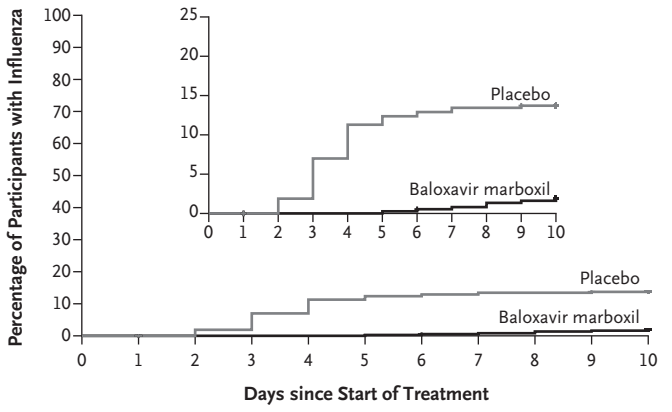

Figure 1. Cumulative Percentage of Participants with Clinical Influenza in the Modified Intention-to-Treat Population.

According to entries in the participant's diary, the onset of clinical influenza was defined as the first recording of either an axillary temperature of at least 37.5°C or a moderate or severe symptom score for cough or nasal discharge, congestion, or both, regardless of the timing of the detection of positivity on reverse-transcriptase–polymerase-chain-reaction assay after the receipt of baloxavir or placebo. The modified intention-to-treat population included all the participants who had undergone randomization and for whom postenrollment data regarding symptom and virologic features were available. The inset shows the same data on an enlarged y axis.

the virus types and subtypes were concordant between the index patients and their household contacts (Table S2).

POSTEXPOSURE PROPHYLAXIS EFFICACY

The primary end point of laboratory-confirmed clinical influenza was identified significantly less often among participants in the baloxavir group than among those in the placebo group (7 of 374 [1.9%] vs. 51 of 375 [13.6%]; adjusted risk ratio, 0.14; 95% confidence interval [CI], 0.06 to 0.30; P<0.001). Among the 51 participants in the placebo group who had laboratory-confirmed clinical influenza, the illness occurred by day 5 in 46 (90.2%), whereas the illness occurred after day 5 in all 7 participants in the baloxavir group who had laboratory-confirmed clinical influenza (Fig. 1). Among participants who were initially uninfected and had contact with an index patient with laboratory-confirmed influenza, the risk of influenza was lower among those in the baloxavir group than among those in the placebo group (adjusted risk ratio, 0.13; 95% CI, 0.05 to 0.31) (Table 2).

Subgroup analyses showed similar efficacies of baloxavir prophylaxis regardless of underlying risk factors, vaccination status, and age category of the index patients or infecting influenza A virus subtypes (Fig. S2). The efficacy of baloxavir was somewhat lower among participants younger than 12 years of age (adjusted risk ratio, 0.27; 95% CI, 0.08 to 0.90) than among those 12 years of age or older (adjusted risk ratio, 0.10; 95% CI, 0.04 to 0.28). Baloxavir prophylaxis also led to a lower percentage of participants with RT-PCR–confirmed illness (fever or at least one influenza symptom) than placebo (adjusted risk ratio, 0.24; 95% CI, 0.15 to 0.38) as well as a lower percentage of participants with RT-PCR–confirmed influenza virus infection regardless of fever and symptoms (adjusted risk ratio, 0.43; 95% CI, 0.32 to 0.58) (Table 2). Among participants with RT-PCR positivity at baseline, fever or other influenza symptoms subsequently developed in 5 of 26 (19%) in the baloxavir group and in 21 of 36 (58%) in the placebo group (adjusted risk ratio, 0.34; 95% CI, 0.15 to 0.80). Subgroup analysis that assessed households with multiple participants or a single participant also showed similar efficacy of baloxavir prophylaxis (Tables S3 and S4).

PA SUBSTITUTIONS

No viruses with PA substitutions were detected at baseline in 62 RT-PCR–positive participants or in 114 index patients who had household contacts who were positive for influenza on RT-PCR assay after the administration of baloxavir or placebo (Table S5). PA I38T–substituted virus was detected in 2 participants in the placebo group 2 days after the use of baloxavir rescue treatment for illness due to nonsubstituted A(H3N2) virus. Among 374 participants who received baloxavir, PA I38T/M and PA E23K variant viruses emerged during or after prophylaxis in 10 (2.7%) and 5 (1.3%), respectively (Figs. 2 and 3). Among 20 participants in the baloxavir group who had RT-PCR–confirmed illness (Table 2), 4 had virus with wild-type PA sequence, 8 had PA I38T or PA I38M substitutions, 3 had PA E23K substitutions, and 5 had no sequence data. Four other participants with PA substitutions (2 with PA I38T and 2 with PA E23K) remained asymptomatic. Comparison of the PA and HA sequences in PA-substituted viruses obtained from baloxavir-treated participants and nonsubstituted viruses obtained from the corresponding index patients determined that 13 of 15 pairs were matched but that 2 had multiple base differences in both PA and HA, which

Table 2. Primary and Secondary End Points (Modified Intention-to-Treat Population).*

End Point	Baloxavir Marboxil (N=374)		Placebo (N=375)		Adjusted Risk Ratio (95% CI)
	Participants with End Point	Percentage (95% CI)	Participants with End Point	Percentage (95% CI)	
	no./total no.		*no./total no.*		
Primary end point: laboratory-confirmed clinical influenza†					
In the modified intention-to-treat population	7/374	1.9 (0.8–3.8)	51/375	13.6 (10.3–17.5)	0.14 (0.06–0.30)‡
Among those who had a negative RT-PCR result at baseline and contact with a RT-PCR–positive index patient	5/344	1.5 (0.5–3.4)	39/337	11.6 (8.4–15.5)	0.13 (0.05–0.31)
Among those <12 yr of age	3/71	4.2 (0.9–11.9)	11/71	15.5 (8.0–26.0)	0.27 (0.08–0.90)
Among those ≥12 yr of age	4/303	1.3 (0.4–3.3)	40/304	13.2 (9.6–17.5)	0.10 (0.04–0.28)
Among those with underlying high-risk factors	1/46	2.2 (0.1–11.5)	8/52	15.4 (6.9–28.1)	0.13 (0.02–0.94)
Secondary end points					
RT-PCR–confirmed influenza virus infection regardless of fever and symptoms	49/374	13.1 (9.9–16.9)	114/375	30.4 (25.8–35.3)	0.43 (0.32–0.58)
RT-PCR–confirmed illness§	20/374	5.3 (3.3–8.1)	84/375	22.4 (18.3–27.0)	0.24 (0.15–0.38)
RT-PCR– or seroconversion-confirmed influenza virus infection regardless of fever and symptoms¶	59/374	15.8 (12.2–19.9)	119/375	31.7 (27.0–36.7)	0.50 (0.38–0.66)
RT-PCR– or seroconversion-confirmed illness‖	23/374	6.1 (3.9–9.1)	86/375	22.9 (18.8–27.5)	0.27 (0.17–0.42)
Asymptomatic infection confirmed by RT-PCR assay or seroconversion**	14/374	3.7 (2.1–6.2)	13/375	3.5 (1.9–5.9)	1.08 (0.52–2.27)

* The modified intention-to-treat population included all the participants who had undergone randomization and for whom postenrollment data regarding symptom and virologic features were available. The analyses were prespecified except as noted.

† Laboratory-confirmed clinical influenza was defined as RT-PCR positivity for influenza virus RNA and the presence of both fever (axillary temperature, ≥37.5°C) and at least one respiratory symptom of moderate or greater severity during the period from day 1 to day 10.

‡ P<0.001 for the comparison with placebo.

§ RT-PCR–confirmed illness was defined as RT-PCR positivity for influenza virus RNA plus a body temperature of at least 37.5°C or at least one moderate or severe symptom.

¶ In this post hoc analysis, the percentage of participants with influenza infection, defined as RT-PCR positivity or at least a quadrupling of the influenza-specific antibody titer (seroconversion), was evaluated.

‖ In this post hoc analysis, the percentage of participants with RT-PCR– or seroconversion-confirmed illness, defined as influenza virus infection confirmed by RT-PCR assay or seroconversion plus an axillary temperature of at least 37.5°C or at least one influenza symptom assessed as moderate or severe (score of 2 or 3, respectively, on the four-point trial scale), was evaluated.

** In this post hoc analysis, the percentage of participants with asymptomatic infection confirmed by RT-PCR assay or seroconversion, defined as influenza infection confirmed by RT-PCR assay or seroconversion plus an axillary temperature of less than 37.5°C and influenza symptoms all assessed as absent (score of 0 on the four-point trial scale), was evaluated.

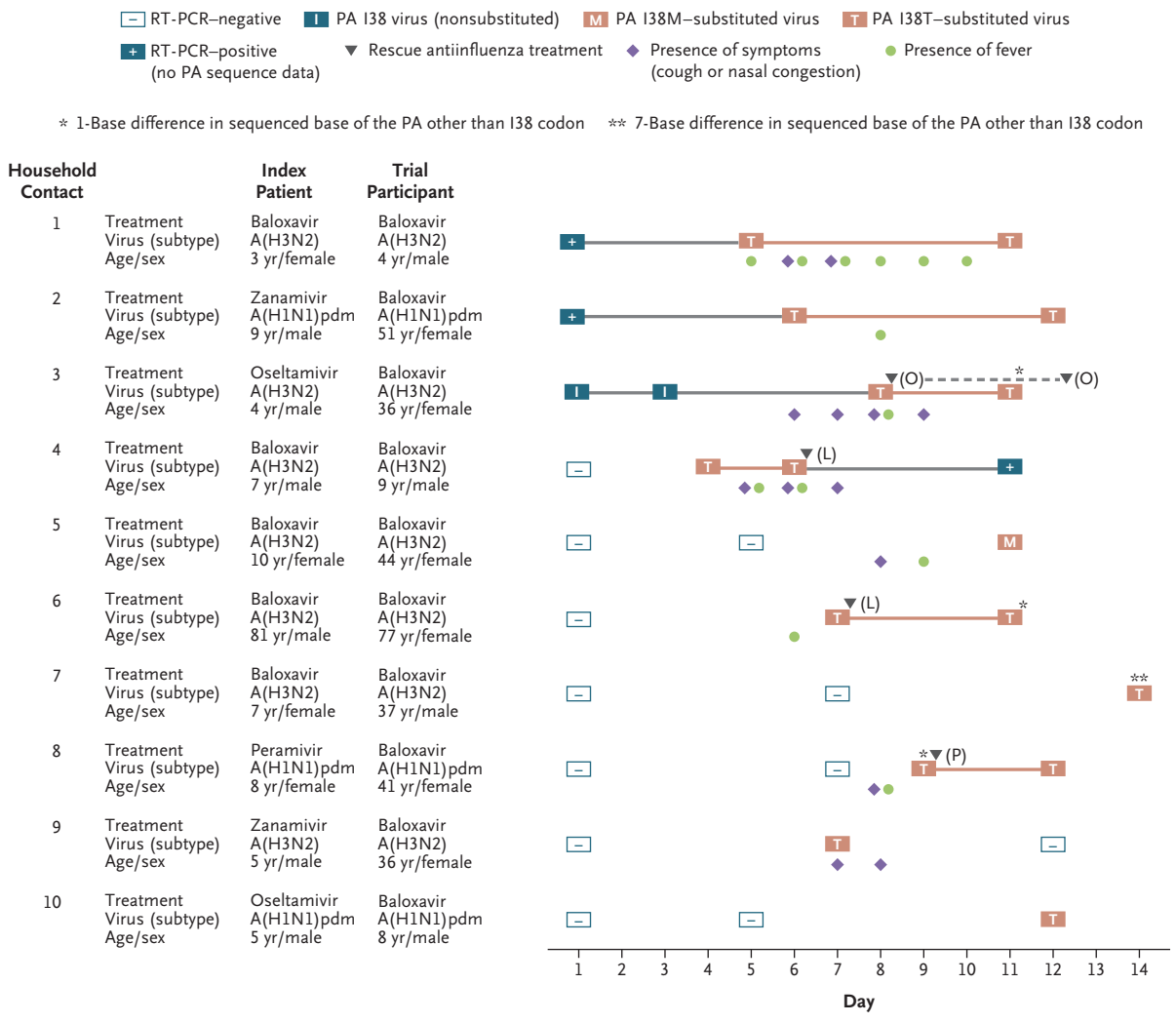

Figure 2. Summary of Emergence of PA I38T/M–Substituted Variant Viruses in Household-Contact Participants Receiving Baloxavir Prophylaxis.

The 10 participants in the baloxavir group in whom polymerase acidic protein (PA) I38T/M–substituted viruses were detected are listed as 1 through 10. Characteristics (age, sex, influenza A subtype, and administration of antiviral agent) of the corresponding household index patients and the contact participants are summarized in the next three columns. The rectangular boxes indicate the days that the sample was obtained and the results on reverse-transcriptase–polymerase-chain-reaction (RT-PCR) testing and PA sequence analysis. Purple diamonds indicate the presence of respiratory symptoms (cough or nasal congestion), and green circles the presence of fever on at least 1 day. The day that another influenza antiviral medication was initiated is indicated by a capital letter denoting the drug administered: laninamivir (L), peramivir (P), or oseltamivir (O). Axillary temperature and presence of symptoms (moderate and severe) were indicated during the observation periods (1 to 10 days). Five participants were exposed to an index patient treated with a neuraminidase inhibitor and 5 to an index patient treated with baloxavir. Except for 1 participant (household contact 7), sequences of hemagglutinin and PA were matched (except for the position 38 corresponding bases) between virus from the participant and virus from the corresponding index patient (Table S6A). Among the 10 participants with PA I38T/M–substituted virus, 3 were RT-PCR–positive at baseline (household contacts 1 through 3). Household contact 1 was exposed to a baloxavir-treated index patient, and household contacts 2 and 3 were exposed to an index patient who had received a neuraminidase inhibitor. Illness developed in all 3 of these participants on days 5 through 8. Among the remaining 7 participants, illness developed in 5 on days 5 through 9 (household contacts 4, 5, 6, 8, and 9). Four participants (household contacts 3, 4, 6, and 8) were treated with a neuraminidase inhibitor as rescue therapy; all had an uneventful recovery. The 1-base difference (asterisk) and the 7-base difference (double asterisk) in PA nucleotide sequence are the differences between the virus from the index patient and that from the corresponding household contact.

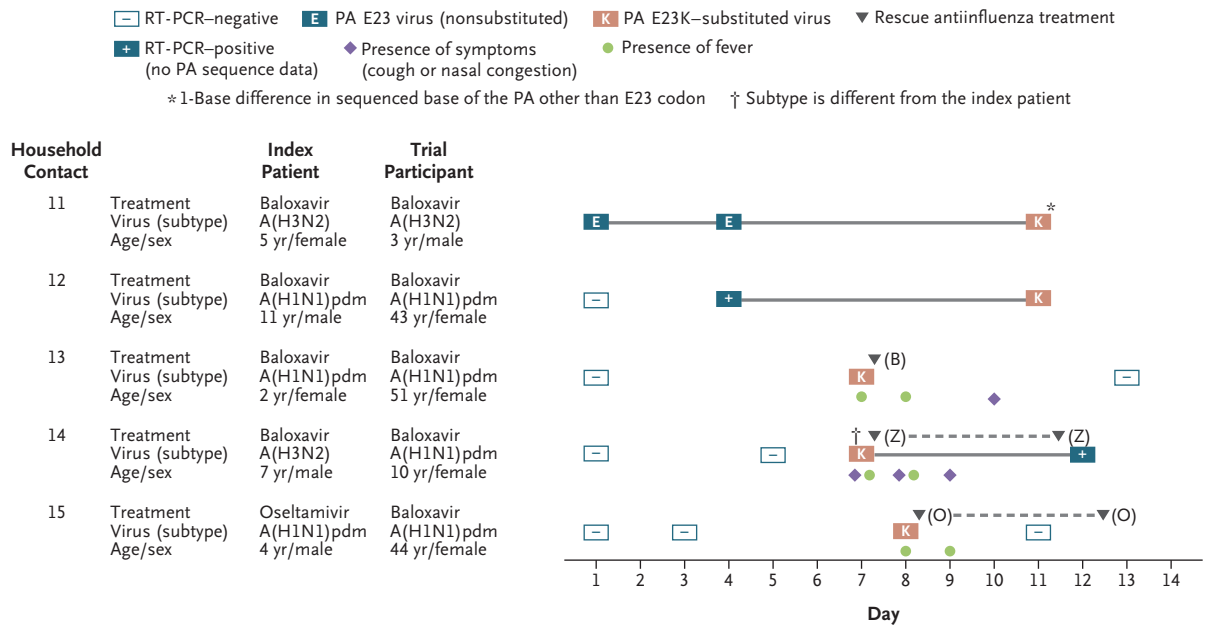

Figure 3. Summary of Emergence of PA E23K–Substituted Variant Viruses in Household-Contact Participants.

The five participants (1.3%) in the baloxavir group in whom PA E23K–substituted viruses were detected are listed as household contacts 11 through 15. Influenza developed in three household contacts (13 through 15) with PA E23K–substituted viruses on days 7 through 10. Four household contacts (11 through 14) were exposed to a baloxavir-treated index patient, but one (household contact 11) had baseline detection of nonsubstituted A(H3N2) virus, and another (household contact 14) was infected by an influenza A subtype that was different from that in the index patient (dagger). The day that another influenza antiviral medication was initiated is indicated by a capital letter denoting the drug administered: baloxavir (B), zanamivir (Z), or oseltamivir (O); all had an uneventful recovery. The 1-base difference in PA nucleotide sequence (asterisk) is the difference between the virus from the index patient and that from the corresponding household contact.

indicated likely acquisition from a source outside the household (Table S6).

ADVERSE EVENTS

Adverse events during the trial were reported in 22.2% of the participants who received baloxavir and in 20.5% of those who received placebo (Table 3). One serious adverse event, atypical psychosis, developed in one participant in the placebo group. The most common adverse events were headache, hematuria, pharyngitis, and increases in the alanine aminotransferase level. Among six participants who received baloxavir and had hematuria detected by dipstick (all female), one had an event that was judged by the investigator as being related to baloxavir (Table S7).

DISCUSSION

This randomized, placebo-controlled clinical trial showed that rapid administration of single-dose baloxavir as postexposure prophylaxis was highly effective in preventing influenza in the household setting and was associated with an incidence of adverse events similar to that with placebo. Baloxavir prophylaxis was effective in high-risk participants, in children younger than 12 years of age, and in unvaccinated participants. Baloxavir not only showed prophylactic efficacy in participants who had not been infected at baseline but also reduced the risk of symptom development among those who were already infected. The overall percentage of participants with laboratory-confirmed influenza virus infection was lower by approximately 50% in the baloxavir group than in the placebo group (Table 2). Relative to earlier randomized, placebo-controlled clinical trials of postexposure prophylaxis with neuraminidase inhibitors, which had somewhat differing trial designs and end points, the point estimate of protective efficacy of baloxavir against laboratory-confirmed clinical influenza in the current trial

Table 3. Incidence of Adverse Events (Safety Population).*

Event	Baloxavir Marboxil (N=374)	Placebo (N=375)
	number (percent)	
Any adverse event	83 (22.2)	77 (20.5)
Event reported in ≥1% of participants in either group		
Nasopharyngitis	24 (6.4)	25 (6.7)
Pharyngitis	4 (1.1)	1 (0.3)
Headache	8 (2.1)	6 (1.6)
Microscopic hematuria†	6 (1.6)	1 (0.3)
Increase in alanine aminotransferase level	4 (1.1)	1 (0.3)
Event related to baloxavir or placebo		
Any event	7 (1.9)	6 (1.6)
Headache	0	1 (0.3)
Nausea	2 (0.5)	0
Diarrhea	1 (0.3)	1 (0.3)
Vomiting	0	1 (0.3)
Abnormal hepatic function	1 (0.3)	1 (0.3)
Rash	1 (0.3)	0
Pyrexia	0	1 (0.3)
Microscopic hematuria†	1 (0.3)	0
Decrease in total protein level	1 (0.3)	0
Increase in alanine aminotransferase level	0	1 (0.3)
Increase in aspartate aminotransferase level	0	1 (0.3)
Death	0	0
Serious adverse event of typical psychosis	0	1 (0.3)

* The safety population included all the participants who had undergone randomization and received one dose of baloxavir or placebo. The mean (±SD) follow-up was 18.8±6.5 days in the baloxavir group and 18.1±4.3 days in the placebo group. The relationship of the adverse event to baloxavir or placebo was determined by the investigator under blinded conditions.

† Microscopic hematuria was determined on dipstick testing; details are provided in Table S7. All the participants with microscopic hematuria were female. An analysis of all previous studies of baloxavir published to date[17,18,22] showed that 5 of 1747 recipients (0.3%) of baloxavir, 3 of 1136 recipients (0.3%) of placebo, and 3 of 1234 recipients (0.2%) of oseltamivir had microscopic hematuria detected.

(86%) compares favorably with that reported for oseltamivir (68 to 89%),[8,9] inhaled zanamivir (82 to 84%),[10,11] and inhaled laninamivir (46 to 78%).[12-14] Previous clinical trials of inhaled zanamivir, oseltamivir, and, when circulating viruses were susceptible and index cases were not treated, amantadine showed that postexposure prophylaxis efficacy in households was associated with efficacy in seasonal prophylaxis and nosocomial outbreak control.[27-34] Our findings in the current trial predict that baloxavir also would be effective for prophylaxis in other nonhousehold settings, although formal clinical trials of multiple dose regimens are required for confirmation.

Influenza transmission in households, especially from child to sibling or adult, is considered to be an important driver in outbreaks.[8] Higher frequencies of influenza occur among children than among adults within households,[35] in part related to lower specific immunity, transmission in nurseries or schools, and perhaps less attention to infection-control measures. In our trial, 73.6% of the index patients and 19.0% of the prophylaxis participants were younger than 12 years of age, and a higher incidence of symptomatic influenza was observed among children than among older household participants in both the baloxavir group and the placebo group. Baloxavir prophylaxis resulted in a significantly lower risk of clinical influenza in pediatric participants than placebo (Fig. S2), but as previously observed with oseltamivir,[8] its protective efficacy was lower than that in teenagers and adults.

Previous studies of baloxavir have detected frequent emergence of PA I38T/M/S/F–substituted viruses in baloxavir-treated patients, especially in children.[21,22] In addition, transmission of such variants to close contacts has been reported, including in the household setting.[24,25] PA I38T–substituted virus emerged in 2 participants in the placebo group in our trial, but only after they had received rescue treatment with baloxavir because of influenza symptoms. No such variants were observed among participants in the placebo group who did not receive rescue treatment with baloxavir, 31.7% (119 of 375) of whom were exposed to baloxavir-treated index patients who were younger than 12 years of age. An ongoing randomized clinical trial (ClinicalTrials.gov number, NCT03969212) is examining the potential of baloxavir treatment of index patients to reduce influenza spread to contacts and is investigating the risk of transmission of PA-substituted viruses.

In the baloxavir group, among the 10 participants with the PA I38T/M variant and the 5 with the PA E23K variant, 4 infections occurred before baloxavir administration (2 with proven nonsubstituted virus) and 4 other infections were associated with index patients who had been treated with a neuraminidase inhibitor. Consequently, these infections were likely initiated by wild-type

virus with subsequent emergence of PA-substituted virus under the selective pressure of baloxavir. However, among the other 7 participants in the baloxavir group, we could not rule out the possibility of transmission of PA-substituted virus from the baloxavir-treated index patient (in 5 participants) or from baloxavir-treated contacts outside the household (in 2 participants). Among 15 participants in the baloxavir group in whom PA-substituted viruses were detected, 11 cases of prophylaxis failure (RT-PCR positivity and fever or influenza symptom) were observed. Such viruses retain susceptibility to neuraminidase inhibitors; thus, patients who have treatment failure with baloxavir prophylaxis could receive rescue neuraminidase inhibitor treatment if it were clinically warranted.

An important limitation of our trial was that follow-up samples were not obtained from the index patients, so the frequency of emergence of resistant variants after baloxavir administration in these patients could not be determined. In addition, PA sequence data could not be obtained in samples from several participants in the baloxavir group in whom illness developed despite prophylaxis. We also could not assess the prophylactic efficacy for influenza B virus because circulation of this virus was limited in our single-season trial. The therapeutic efficacy of baloxavir has been shown in high-risk outpatients with influenza B virus infection, in whom baloxavir treatment was associated with greater antiviral and clinical effects than placebo or oseltamivir.[18] These findings suggest that baloxavir could be effective for prophylaxis against influenza B, but additional studies are required. We did not capture data regarding the time from the onset of illness in the index patient to the initiation of prophylaxis in the household contacts, but the substantial proportion of participants with RT-PCR positivity at enrollment and the rapid occurrence of illness in participants in the placebo group (Fig. 1) emphasize the need for prompt initiation.

In conclusion, a single oral dose of baloxavir was highly effective in preventing influenza in household contacts and was associated with a safety profile similar to that of placebo. Influenza developed in a small number of participants who received baloxavir prophylaxis, and in some cases it was associated with the emergence of virus variants with PA amino acid substitutions. The positive findings with baloxavir prophylaxis in reducing the spread of influenza virus within households suggest the need for studying its prophylactic efficacy in other nonhousehold settings.

Supported by Shionogi.

Dr. Ikematsu reports receiving lecture fees from Daiichi Sankyo and lecture fees, consulting fees, and travel support from Shionogi; Dr. Hayden, receiving fees for serving on a data safety and monitoring board, paid to the University of Virginia School of Medicine, from Celltrion Healthcare, GlaxoSmithKline, and Vaccitech, serving as a consultant and receiving travel support from F. Hoffmann–La Roche and Shionogi, and serving as a consultant for Cidara Therapeutics, Fujifilm Corporation, Genentech, Gilead Sciences, Janssen Pharmaceuticals, MediVector, Regeneron Pharmaceuticals, resTORbio, SAB Biotherapeutics, Versatope, Vir, and Visterra; Drs. Kawaguchi, Noshi, and Uehara, being employed by Shionogi; Drs. Kinoshita, Takashima, and Tsuchiya, being employed by and owning stock in Shionogi; Dr. de Jong, receiving advisory board fees from Cidara Therapeutics and F. Hoffmann–La Roche and fees for serving on a data and safety monitoring committee from Janssen Pharmaceuticals; and Dr. Lee, receiving consulting fees from Cidara Therapeutics, F. Hoffmann–La Roche, Janssen Global Services, and Sanofi Pasteur and travel support from Shionogi. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank all the participants; Toru Ishibashi, Satoshi Kojima, Takafumi Hara, Keiko Baba, and Takao Shishido (all from Shionogi) for assistance in preparing technical support documents and an earlier version of the manuscript after the initial draft; and the staff of LSI Medience for conducting reverse-transcriptase–polymerase-chain-reaction analyses and polymerase acidic protein sequencing of swab samples.

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